A Therapeutic and Economic Assessment of Betaseron® in Multiple Sclerosis

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Cost/Effectiveness Modelling and Implementation
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Note - This 2003 pdf version of the original report has been slightly modified for consistency of style and ease of use. No substantive changes have been made. The numbering of some tables has been changed.
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Assistance in assembling data and undertaking analyses was provided by the staff of the Dalhousie Multiple Sclerosis Research Unit and by research assistants Chris Skedgel, Pat Randel, Mark Smith, Kelly McLean and Linda Awalt.

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<tr>
<td>CCOHTA</td>
<td>Canadian Coordinating Office for Health Technology Assessment</td>
</tr>
<tr>
<td>C/E</td>
<td>cost/effectiveness ratio</td>
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<tr>
<td>C/E&lt;sub&gt;nEDSS-DYA&lt;/sub&gt;</td>
<td>Cost / nEDSS-DYA avoided; a C/E ratio where E is measured by normalized EDSS-weighted-disability-years avoided (nEDSS-DYA); a 'normalized' or rescaled EDSS = nEDSS = EDSS/10, range 0 = good health to 1.0 = death due to multiple sclerosis.</td>
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<td>C/U&lt;sub&gt;EQ-5D-QALY&lt;/sub&gt;</td>
<td>cost / EQ-5D-QALY gained; a C/U ratio where U is a generic health index measured in EuroQols using EQ-5D methods; range 1.0 = good health to 0.0 = death.</td>
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<td>C/U&lt;sub&gt;GENERIC-QALY&lt;/sub&gt;</td>
<td>cost / GENERIC-QALY gained; a C/U ratio where U is measured using a generic health index; range 1.0 = good health to 0.0 = death.</td>
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<tr>
<td>cp</td>
<td>chronic progressive</td>
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<tr>
<td>C/U</td>
<td>cost / utility ratio</td>
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<tr>
<td>DOH</td>
<td>Department of Health, Province of Nova Scotia</td>
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<td>DMSRU</td>
<td>Dalhousie Multiple Sclerosis Research Unit</td>
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<td>EDSS</td>
<td>(Kurtzke) Expanded Disability Status Scale</td>
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<tr>
<td>MS</td>
<td>multiple sclerosis</td>
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<td>MSI</td>
<td>Medical Services Insurance programs, Nova Scotia</td>
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<td>MSID</td>
<td>multiple sclerosis integrated database</td>
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<td>PwMS</td>
<td>person(s) with multiple sclerosis</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>rr</td>
<td>relapsing/remitting</td>
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See Appendix B for a detailed glossary of abbreviations used in Spreadsheet Tables used to compute C/E and C/U estimates.
MS Classification Systems

For many years MS has been classified according to the initial pattern at the onset of the disease. Patients often had a pattern of acute attacks and remissions (relapsing-remitting), or might begin or progress to a pattern of attacks with some residual symptoms and some progression over the years (relapsing-progressive). Other patients, especially those with a late onset of the disease, might show a slowly progressive pattern from the beginning, without any acute attacks (chronic progressive). In about 20% of cases there is a pattern of relapsing-remitting symptoms, with mostly sensory symptoms, but little progression over ten or twenty years (benign). A separate group comprises those cases with isolated optic neuritis or transverse myelitis, who turn out later to have MS in a high percentage of cases, but as yet have no further evidence of the disease. (optic neuritis; transverse myelitis)

In recent years, a regrouping of these cases according to initial onset has occurred in some studies, but the groups are overlapping, and cause no confusion about what patients are involved. For instance, those who have an onset with acute attacks (relapses), whether they are relapsing-remitting or relapsing progressive can be grouped (bout onset), whereas those with a progressive onset form the start are in another group (progressive onset). The only confusion is the use of different terminology, and we hope that in further trials there will be an accepted terminology used by everyone.

<table>
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<tr>
<td>relapsing-remitting</td>
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<td>secondary progressive</td>
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<tr>
<td>relapsing-progressive</td>
<td>acute onset</td>
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<td>optic neuritis</td>
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<td>transverse myelitis</td>
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<tr>
<td>chronic progressive</td>
<td>progressive onset</td>
<td>primary progressive</td>
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<td>benign</td>
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In some trials they have grouped the patients who show progression from the start as 'primary progressive', while those with an onset with acute attacks but later progress, as 'secondary progression'.

Another element has been added to assist with diagnosis in recent years with the qualification of "laboratory supported" to accompany the "gold standard" of clinical determination. This would apply to a confirmatory test showing oligoclonal banding in the CSF. In recent years the drug trials have included only patients who also have a positive MRI.

One final point related to the understanding of the definition of the terms and consistency in their application. It seems that they are generally understood and applied consistently except for the
category of benign MS. Some current work is underway to achieve a consistent definition of who fits into that category, and how many years of mild disease is required before the title can be applied.
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Copyright Materials

The following have kindly given permission to quote copyrighted or unpublished materials.


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Little, Brown and Company. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI analysis group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995; 45:1278, Figure 1
Pharmacoeconomic Guidelines Summary Checklist

A THERAPEUTIC AND ECONOMIC ASSESSMENT OF BETASERON® IN MULTIPLE SCLEROSIS

1. Description of medical problem. Multiple sclerosis is a disease of the central nervous system characterized by early onset of symptoms (usually by age 35), progressive disability, and near normal life expectancy. Betaseron® is the first drug which appears to alter the natural history of multiple sclerosis (MS) in persons classified as 'relapsing remitting' and having 'mild' disability progression (Extended Disability Status Scale, EDSS<6).

2. Description of the therapy. For persons with a definite diagnosis of relapsing-remitting MS and EDSS<6, subcutaneous injections of 8 MIU Betaseron® every second day indefinitely, or until discontinued.

3. Perspective and target audience. The perspective is public sector, Department of Health. The study was funded by the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) with the primary target audience being provincial departments of health and drug insurance plan administrators.

4. Target population. Persons with MS. Prevalence varies geographically, with greater prevalence in higher latitudes, in the order of 100 per 100,000 or 1/10th of 1% in Canada and Belgium. The ratio of females/males with MS ranges from about 2/1 to 3/1.

5. Comparator. MS natural history, or placebo.

6. Treatment path. A definite diagnosis of MS typically occurs within two years of onset of symptoms. Authorization to treat with Betaseron® varies across jurisdictions, and may be restricted to specialists and/or MS clinics at present.

7. Analytic horizon. MS natural history, from onset of symptoms to 40 years after onset or death.

8. Analytical technique. Cost-effectiveness (C/E) analysis of disability progression. Treatment outcomes (E) are expressed as normalized EDSS-weighted-Disability-Years-Avoided (E_{nEDSS-DYA}). Hypothetical cohorts of 1,000 females and 1,000 males are analysed within a spreadsheet model of MS natural history, from onset to 40 years after onset or death.

9. Data sources and research design. MS natural history data on EDSS disability progression to EDSS=6, by MS classification and gender, originates from a Swedish study of an MS onset cohort of 308 persons followed for 25 years. (Runmarker and Anderson 1993) Betaseron® efficacy data on slowing EDSS progression and reducing exacerbation rates and MRI measured disease activity originate from a single randomized controlled trial (IFNB 1993, 1995) Public sector health care costs by persons with MS, stratified by MS classification and
disability severity, from a study of MS Health Care Costs in Nova Scotia. (Brown et al 1995) Betaseron® treatment costs are based on approved Canadian prices of $91/ 8MIU dose every second day, or $16,685 per person per year.

C/E analyses are developed for a ‘baseline scenario' for females and males classified as relapsing remitting, and for fourteen additional scenarios.

10. Related studies. A literature review of alternative drug therapies for MS concluded that the appropriate comparator for Betaseron® treatment was MS natural history.

11. Identification and measurement of costs. Public sector health care costs measured in Nova Scotia included physicians services, hospital services (inpatient and outpatient) and Seniors' Pharmacare services for persons 65 years old or more. These services are tax financed health care programs which cover all citizens of Nova Scotia, have very comprehensive coverage of services, and are ‘free' at point of utilization, except for co-payment charges under the Seniors' Drug program. Costs for persons with MS were derived by linking (anonymized) records from the Dalhousie (University) MS Research Unit (DMSRU) to Nova Scotia administrative databases for their "Medicare" programs. Physician costs are based on fee-for-service claims. Hospital costs are based on hospital admission/separation/day surgery utilization data costed at a fixed $500 CDN per diem charge. Other public sector and private sector costs were not included in the C/E analyses. These would include public sector social services costs, private sector direct care costs, costs of lost time by persons with MS and caregivers, and other MS-related special costs.

12. Identification and measurement of outcomes. The outcomes analysed are based on Betaseron® RCT results. Outcomes measured included reduced exacerbation rates, reduced disease activity (by MRI) and slower EDSS disability progression. RCT treatment efficacy data for EDSS progression were used with MS natural history data on EDSS progression to estimate normalized EDSS disability years avoided (E_nEDSS-DYA) due to treatment. A highly exploratory analysis expressed these MS-specific health outcome measures in terms of a generic-QALYS. This exercise indicated that the relatively narrow EDSS measure of MS disability progression likely understates treatment benefits, which means that C/E estimates based on EDSS disability years avoided, or EDSS-QALYS, will be larger than C/E estimates where outcomes are expressed in terms of generic-QALYS.

13. Valuation of costs. See 11.

14. Valuation of outcomes. For purposes of analysis the EDSS was assumed to have additive properties. For purposes of weighting disability-years-avoided (DYA) due to treatment, normalized EDSS weights (range 0 - 1) were used (nEDSS = EDSS/10).

15. Discounting rates for costs and outcomes. Costs and outcomes were discounted at 0% and 5% in thirteen scenarios, and at 2.5% and 7.5% in two other scenarios.

16. Summary results for females and males are presented in within the body of the report (Table 4) while detailed results for ‘baseline scenario #1’ are presented in appendices. MS-
specific C/E results expressed as normalized EDSS disability years avoided are not directly comparable with published C/E results based on generic QALYS. Even after allowing for differences in measurement methods, however, C/E estimates for Betaseron® in MS appeared to fall in the middle to upper part of the distribution of C/E estimates for the treatment of other diseases.

17. Uncertainty. C/E estimates are subject to great uncertainty given that only short run (5 year) RCT data on efficacy are available for an analysis of treatment effects and costs which are spread over the long natural history of MS. The consequences of different models of MS progression and of different assumptions about treatment effectiveness, eligibility for treatment policy, MS management, patient compliance and costs are explored in various scenarios.

18. Sub-Group Analyses. Sub-groups analysed are females, males, relapsing remitting and chronic progressive persons with MS.

19. Equity. Normalized EDSS-weighted-Disability-Years-Avoided (EnEDSS-DYA) are assumed to be valued equally by all persons with MS.

20. Disclosure and relationships. The research was sponsored by CCOHTA, an information gathering and dissemination body created by the federal and provincial governments of Canada.

21. References. Extensive references are given in the report.

22. Appendices. Detailed spreadsheet tables for the baseline scenario are presented in an appendix, for females and for males. Summary tables containing C/E estimates from 500 studies of life saving interventions are also presented in an appendix.
EXECUTIVE SUMMARY

A THERAPEUTIC AND ECONOMIC ASSESSMENT OF BETASERON® IN MS

Betaseron® treatment in MS is of interest because in a well-designed randomized double blind controlled trial (RCT) it was shown to favourably alter the natural history of MS in the short run, thereby giving hope to Persons with MS (PwMS). Betaseron® is also a very expensive drug, and MS is characterized by early onset and a near normal life expectancy.

Therapeutic Assessment In a three year study of PwMS classified as “relapsing-remitting” the number and severity of attacks (exacerbations) was reduced by up to 24% - 33% in the 8 MIU treatment group compared to placebo. Given an exacerbation rate of 1.27 per patient per year in the placebo group, treatment may avoid one exacerbation every two to three years. Treatment also reduced MS disease activity as measured by annual MRI scans of the number and area of lesions, with a 3.6% increase in the 8 MIU treatment group compared to 18.7% in the placebo group. Correlations of MS disease activity and various manifestations of MS symptoms, however, are generally weak and poorly understood. Statistical significance at better than the 5% level was achieved for both exacerbation effects and disease activity effects. Neutralizing antibodies were detectable in 38% of patients by the third year, however, and were associated with a significant attenuation of treatment effect on exacerbation rates. (IFNB MS Study Group, 1993).

The RCT was extended to five years to examine possible treatment effects on MS disability progression, measured by time elapsed until a one-point progression on the Expanded Disability Status Scale (EDSS) was observed. MS disability progression was up to 15% slower in the 8 MIU treatment group compared to placebo, but statistical significance was only at the 10% level. (IFNB MS Study Group, 1995).

Assessment of the potential benefit of this therapy to persons with MS (PwMS) is problematic since none of the RCT outcome measures fully captures the burden of this complex disease. Assessment of therapeutic benefit over the long natural history of MS is fraught with uncertainty given availability of only short run evidence from a single RCT which had considerable loss of participants by year 5.

Direct Treatment Costs Direct treatment costs, based on $91.427 per 8 MIU treatment every second day (365/2), total $16,685 CDN annually per person treated. The size of estimated health costs foregone due to treatment is small relative to the size of direct treatment costs.

Cost per Exacerbation Episode Avoided Given avoidance of one exacerbation episode every 2 to 3 years and direct treatment costs of $16,685 per year, the cost per exacerbation episode avoided may lie between $33,000 and $50,000. Ambulatory direct care treatment costs for an
exacerbation episode are estimated to cost approximately $422 in Nova Scotia while inpatient hospital care would cost about $4500.

**Cost per Disability Year Avoided**

A Cost/effectiveness (C/E) ratio may be written as:

\[
C = \frac{\text{net treatment costs}}{\text{treatment costs} - \text{costs foregone}}, \\
E = \frac{\text{net health benefits}}{HS(t) - HS(nt)}
\]

where C represents net (incremental) treatment costs, comprised of Betaseron® direct treatment costs less health care costs foregone, and E represents net health benefits from efficacious treatment which raises health status (HS) from HS(nt), health status given no treatment, to HS(t), health status given treatment. The natural history of MS is adopted as the appropriate time frame for analysing Betaseron® treatment effects on MS progression, given early age of MS onset and near normal life expectancy. Over a long 40-year natural history of MS, treatment effects are summarized by measures which weight each year subsequent to onset of MS symptoms by the disability (EDSS) experienced in that year.

In assessing Betaseron®, using EDSS points to measure MS disease progression, treatment effectiveness (E) is measured by 'normalized EDSS-weighted-Disability-Years-Avoided' (nEDSS-DYA, or \(E_{nEDSS-DYA}\)) over the natural history of MS. Cost/effectiveness is measured by \(C/E_{nEDSS-DYA}\), and estimates are reported using 0% and 5% discount rates. Betaseron® program costs (C), \(E_{nEDSS-DYA}\) and \(C/E_{nEDSS-DYA}\) ratios are estimated for 15 scenarios, by gender, using a single EDSS=6 endpoint model and adopting a department of health perspective. Revised \(E_{nEDSS-DYA}\) estimates rise by about 66% and revised \(C/E_{nEDSS-DYA}\) estimates fall by about 50%, using EDSS=3 and EDSS=6 to model MS progression and higher EDSS means for the 'severely' disabled. Revised estimates for females classified as relapsing-remitting MS are reported below.

**Estimated Disability Years Avoided** (\(E_{nEDSS-DYA}\) Over the Natural History of MS)

In baseline Scenario #1 a 15% treatment effect is estimated to yield about 1.4 nEDSS-weighted Disability-Years-Avoided per female over the 40 years following onset of MS symptoms. This represents about a 10% reduction of total disability years expected over the natural history of MS. The present value of outcomes at time of onset, discounting at 5%, is 0.5 nEDSS-DYA per female, about a third of the undiscounted estimate. Estimates for males are fairly similar.

**Estimated Betaseron® Program Costs**

Betaseron® direct treatment costs of $16,685 per PwMS per year dominate estimated public sector health care costs foregone. Direct treatment costs per female, over a 40-year period of analysis, total $390,145 in current dollars or $198,584 when discounted at 5%. Direct treatment costs per male are about 8% lower.

**Estimated \(C/E_{nEDSS-DYA}\) Ratios**

The estimated \(C/E_{nEDSS-DYA}\) ratio for Scenario #1 for is about $219,000 per nEDSS-DYA for females, expressed in current CDN dollars, where all rr PwMS with EDSS<6 are eligible for treatment until EDSS=6 is reached. On a present value basis at time of MS onset, estimated \(C/E_{nEDSS-DYA}\) increases to about $326,000 using a 5% discount rate. Discounted \(C/E_{nEDSS-DYA}\) estimates are greater than undiscounted C/E estimates because Betaseron® treatment costs begin soon after onset of MS symptoms, whereas treatment
benefits and costs foregone due to delayed progression occur years later. Estimated $C/E_{nEDSS-DYA}$ for males are about 17% lower than those for females.

$C/E_{nEDSS-DYA}$ estimates for Scenarios #2 - #5 are greater than those for baseline Scenario #1, as treatment eligibility policies, compliance rates, discontinuance of treatment due to antibody buildup, and co-payment charges are introduced. The major impact of such changes is on total program costs, through changes in number of PwMS treated, rather than on $C/E_{nEDSS-DYA}$ ratios. Estimated $C/E_{nEDSS-DYA}$ ratios double in Scenario #6, where the treatment efficacy is reduced from 15% to 7.5%, and $C/E_{nEDSS-DYA}$ ratios would continue to rise if the treatment efficacy were modelled to be even lower.

**Converting $C/E_{nEDSS-DYA}$ Estimates To $C/U_{GENERIC-QALY}$ Guesstimates** In order to compare C/E estimates both within and across disease areas it would be desirable to assess Betaseron® treatment outcomes using a generic QALY measures of effectiveness, rather than an MS-specific measures such as nEDSS-DYA. An exploratory simulation which maps “mild” and “severe” EDSS scores to a generic-QALY score (using EuroQol EQ-5D) suggests that estimated Betaseron® treatment effects on MS progression may be substantially larger when measured using a generic-QALY index rather than a narrower MS-specific index. If so, C/E estimates for Betaseron® in MS, expressed using generic-QALYs, will be lower than estimates expressed as $C/E_{nEDSS-DYA}$, by perhaps 25% or more.

Even after Betaseron® $C/E_{nEDSS-DYA}$ revised estimates from a department of health perspective are expressed as $C/U_{GENERIC-QALY}$ gained, they may still fall in the middle to upper part of the distribution of comparable $C/U_{GENERIC-QALY}$ estimates for treatments in other disease areas. However, Betaseron® C/E estimates would be revised downward again in an analysis conducted from a societal perspective, which incorporated all public and private sector costs foregone.

**Program Costs in the Short and Long Run** Betaseron® program costs per PwMS at risk will be much greater in the short run than in the long run. Demand for treatment may be high initially, but will likely decline as compliance rates fall. Compliance studies find fairly rapid declines in compliance, with long-term rates for non-life-threatening conditions approaching 20%. The licensing of competing pharmacotherapies for MS will reduce the cost of Betaseron® treatment programs, through price reductions and loss of market share, but may not reduce the combined cost of all MS treatment programs.

**Concluding Comments** Evidence of Betaseron® effectiveness in MS, and its subsequent release for general use, has been a very heartening experience for clinicians who manage MS patients, and for persons with MS and their families. Although it is not “the answer”, it is the first drug released that appears to have an effect on the outcome of the disease and so is an important first step.
A THERAPEUTIC AND ECONOMIC ASSESSMENT OF BETASERON® IN MULTIPLE SCLEROSIS

This study’s objective is “To conduct a therapeutic and economic assessment of Betaseron® (interferon beta-1b: Berlex) in Multiple Sclerosis.” The study was commissioned by The Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

I THERAPEUTIC ASSESSMENT

1.1 Significance of Clinical and MRI Effects of Betaseron® in MS

Betaseron® is of interest because in a well-designed randomized double blind controlled trial (RCT) it was shown to have an effect on the number and severity of attacks (exacerbations) of the disease, and to reduce the white matter changes on Magnetic Resonance Imaging (MRIs) (IFNB MS Study Group, 1993). There is additional information that disability may be decreased over five years (IFNB MS Study Group, 1995). An early assessment of the potential benefit of this therapy must be based on how well these measures assess the progression and impact of this disease.

MS affects patients in many ways, all of which are important, but only some of these are measured by clinicians and by clinical studies. For instance, MS affects mobility, which can be measured and quantified, and is one of the most important and prominent features of the disease. Decreased mobility, the major aspect of impairment and disability in these patients, is a routine part of the clinical assessment of these patients. Mobility is a prominent element in the Kurtzke Scale, which forms the basis of the Expanded Disability Status Scale (EDSS) instrument commonly used in clinical trials. Other effects of the disease, such as altered self-image, changed life plans, lost opportunities, altered relationships and marital strains, may be equally important, but are not usually measured in clinical studies of the effects of therapeutic agents. To some extent, the easily quantifiable effects of the disease, such as gait, weakness, sensory loss, need for walking aids, visual change, bladder control, and mental and emotional change are a proxy for the other psychosocial effects noted above. One can infer that improvement in aspects captured by the EDSS will have some impact on altered self-image, social and sexual relations and other aspects important to patients.
The protocol for the Betaseron® studies, like all therapeutic studies in MS in recent years, placed
great emphasis on the diagnostic criteria, the elements of neurological dysfunction as defined on
a standard neurological examination and classified by the Scripps Neurologic Rating Scale, and
the EDSS. Most, if not all, studies of new drugs for MS use similar instruments. Although
course, and with limitations for measuring the overall effects of the disease, these assessments
have strengths in being reproducible, widely accepted, used in virtually every study of MS, and
capturing the major features of the disability resulting from the disease.

1.2 Review of Betaseron® RCT Evidence

One well-designed clinical trial of Betaseron® in patients with MS with sufficient power to
demonstrate measurable clinical and laboratory effects has been reported. This trial was
followed by FDA approval for this drug in the management of MS. Given the importance of this
trial in providing estimates of efficacy, and the pivotal use of these estimates in this C/E analysis,
the methods and outcomes of this trial are reviewed below in detail.

The IFNB (interferon beta-1) Multiple Sclerosis Study Group and the British Columbia MS/MRI
Analysis Group reported 2 and 3-year data (IFNB 1993) and a final report (IFBN 1995) on
Betaseron® RCT results. The patients in the three arms of the trial had been studied for a median
of 46 months (placebo), 45 months (1.6 MIU) and 48 months (8 MIU).

1.2.1 Trial Methods

Three hundred and seventy-two subjects with clinically definite or laboratory-supported multiple
sclerosis were enrolled in a five-year double blind randomized controlled trial comparing
Betaseron® to placebo. These patients had relapsing/remitting MS with a mean duration of 4.4
years and were ambulatory. They were randomized to a placebo group, a “low-dose” Betaseron®
group (1.6 MIU), and a “high-dose Betaseron® group (8 MIU). They had relapsing-remitting MS
with at least two acute exacerbations in the two years before entry into the trial, were between
the ages of 18 and 50 and had EDSS scores of 5.5 or less. The authors employed a modified
intention-to-treat analysis, not further described in the published report. From their description of
their analyses, it appears that data were used until the point of study completion, dropout or
progression in disability due to multiple sclerosis. The principal outcome measures were the
annual exacerbation rate and the proportion of exacerbation-free subjects. Secondary measures included progression in disability, the number and size of central nervous system lesions as detected by MRI scans, and the presence of serum neutralizing antibodies to Betaseron®. The authors used the Kurtzke expanded disability status scale (EDSS) to measure MS-related disability, and defined progression in disability as an increase in EDSS by one point confirmed at two visits at least 3 months apart. Severity of exacerbations was assessed using the Scripps Neurologic Rating Scale (NRS). Severities of exacerbations were either unknown or classified by the NRS as mild, moderate, severe. Radiologists blinded to the patient’s identity assessed the percentage change in lesion area as detected by MRI.

EDSS, NRS and neutralizing antibodies were assessed at each of the quarterly visits per year and MRI scans were performed yearly. Although reasons for discontinuing the trial were well documented and reported, dropouts were not systematically tracked. Statistical analyses included analysis of variance based on ranks for the continuous variables, Kaplan-Meier survival analysis curves with log-rank tests comparing the length of time before onset of the first and second exacerbations as well as the probability of not progressing in disability, and Spearman rank correlations among the primary and secondary outcome measures (IFNB Multiple Sclerosis Study Group, 1993, p. 657; IFNB Multiple Sclerosis Study Group, 1995, p. 1278)

1.2.2 Treatment Effects: Interpretation and Limitations

1.2.2.1 Exacerbation Rates

Exacerbations, measured as mild, moderate, severe or unknown by the Scripps Neurologic Rating scale (NRS), were converted into annual rates for each arm, based on the actual length of time in the study for each subject. Rates for all three arms decreased over the length of the study, consistent with the natural history of relapsing-remitting multiple sclerosis, but for each study year, the 8 MIU group maintained a 24 to 33% lower rate than the placebo group. This was statistically significant in years one and two only.

Is it reasonable to assume that this ¼ to ⅕ difference in annual exacerbation rates seen in the 8 MIU Betaseron® group is accurate and the same for the five years of the trial? The power of this study to detect a ¼ to ⅕ difference in rates decreased each year as both the number of subjects and the number of exacerbations per year dropped, which accounts for the loss of statistical
significance for point estimates for each of the five RCT years. Assuming no other biases, it may therefore be reasonable to assume that the treatment effect persisted. However, this outcome measure is subject to the same bias from dropouts due to perception of worsening as progression in disability, a bias which can be estimated from the information provided. If the 13 subjects in the 8 MIU group and the corresponding 6 in the placebo group who dropped out because of patient or investigator perception of worsening were considered to have a single exacerbation and were counted in year five for example, the new 8 MIU annual exacerbation rate would be 0.64 (58*0.57+13)/58+13 and for the placebo group, 0.82 (56*0.81+6)/56+6. This scenario would reduce the five year decrease in rates due to Betaseron® from the reported 30% to 22% (100-0.64/0.82), a clinically important reduction if this bias were operating but still not enough to cast serious doubt on the persistence of the treatment effect over the five years of the trial.

In summary, the trial provides good evidence of a reduction in annual exacerbation rate in the reported interval of 24 to 33% for at least two years and demonstrates, albeit with less precision, the persistence of this effect over five years.

1.2.2.2 MS Activity, MRI Lesions

Each subject had annual MRI scans interpreted by a blinded radiologist who counted the number of lesions and measured their percentage change from baseline measurements. Of the 372 who were initially randomized, 217 (58%) had either 4 or 5 year MRIs. The median increase in lesion area for placebo patients assessed in year five was 18.7%, compared with 3.6% in the 8 MIU group (p=0.036). This difference was seen for each of the five years. There are no obvious biases to mitigate this effect.

1.2.2.3 Disability Progression

Although EDSS-measured progression in disability is not the principal outcome measure in the initial clinical trial at three years, it is in the extension study of a further two years. It is the primary outcome measure analysed in this therapeutic and economic assessment of Betaseron®.

Kaplan-Meier survival curves were presented showing, by treatment arm, the probability of avoiding progression in disability as defined in the previous section. (Attachment 1) By visual
inspection of the curves, the placebo group was intermediate in progression of disability with the 8 MIU Betaseron® showing the least progression and the 1.6 MIU group showing the most. Compared to placebo, the median time to progression was 15% longer in the 8 MIU group but 17% shorter in the 1.6 MIU. By log-rank test, these differences were not statistically significant at the .05 level, although the p-value for placebo compared to 8 MIU was 0.096. Therefore, one cannot reject the null hypothesis of no difference among the groups although a clinically important increase in median time to progression of 15% was observed.

What are the limitations in interpreting the above results? First, there is a risk of a type II statistical error, i.e., accepting the null hypothesis of no treatment effect when it is false. The authors did not present power calculations but given the p-value of 0.096 for the observed treatment effect of 15%, this trial did not have sufficient power to detect an effect of this size.
Second, there is unquantified measurement error in the assessment of EDSS, which could lead to random noise, bias or both. As noted above in section 1.1, the scales are weighted heavily towards the standard neurological assessment and mobility of the patient and although widely used, have reported limitations. For example, in a well-executed single-blind trial comparing cyclophosphamide ± steroids to placebo, two neurologists did blinded evaluations of EDSS scores every 6 months (Canadian Cooperative Multiple Sclerosis Study Group, 1991, p. 441-6). During simultaneous observations, the monitoring neurologist classified 35 patients as wheelchair-bound compared to 14 for the evaluating neurologist (Weiner, 1991, p. 1033), enough to lead to at least a 0.5 difference in EDSS score for these subjects. The investigators argued that a two-step-change in EDSS score was required because of inter-rater reliability (Noseworthy, 1991, p. 1033-4). If the reliability of assessment was similar in the Betaseron® trial, such measurement error would have led to random misclassification where some subjects who had truly progressed were assessed as stable and others who were stable were assessed as having progressed. This random noise would reduce the power of this trial to detect a treatment effect as measured by a one-point difference in EDSS score.

Biased assessments of EDSS scores are also possible because of the potential of unmasking. The investigators reported an initial rate of flu-like symptoms in the 8 MIU group of 52% compared to 18% in the placebo group and an initial rate of injection site reactions of 80% in the 8 MIU group with no report on the rate in the placebo group, which may have led some subjects and treating neurologists to bias their assessments of elements of the EDSS depending on their belief about their allocation. Fortunately, the evaluating neurologists, different from the treating neurologists by study design and who provided the measures of EDSS for the study, admitted that they did not know the allocation. (IFNB,1993, 660). Bias in assessment of EDSS scores due to unmasking is therefore likely non-existent or clinically unimportant.

The high dropout rate is a more serious contributor to biased assessment of treatment effects using EDSS scores. The investigators appropriately used survival curves to compare progression in disability among the three arms. Observations were censured once patients met the definition for progression in disability. However, 55% of subjects were no longer in the trial at five years and subjects dropped out or were lost for a variety of reasons, some related to side effects and treatment. Evidence that the dropout group is not substantially different is provided by Table 2 (in IFNB MS Study Group, 1995, p. 1279), which shows that for dropouts compared to completers, annual exacerbation rates, changes in EDSS and percent change in MRI lesion area follow the same trend over the three study arms. While the number of dropouts was similar in the
three study arms, as the dose increased, the number of dropouts because of patient or investigator perception of worsening increased substantially (placebo=6, 1.6 MIU=10, 8 MIU = 13). Although not reported in detail, it may be that exacerbations or complications were considerably more severe in these dropouts and would have reduced the measured benefit of the Betaseron® over placebo had the authors been able to measure the EDSS at the time of dropout and included them in the survival curves. A sensitivity analysis assuming that these 30 dropouts had increased one EDSS point would have addressed the possible extent of this bias due to dropout.

In summary, the trial does not provide evidence against the null hypothesis of no Betaseron® treatment effects measured by EDSS progression in disability. The trial lacks power to detect the observed increase in median time to progression of 15%. This observed increase is, if true, clinically important. Misclassification error, insensitivity in the EDSS to small differences in disability of progression, and bias due to nondifferential dropouts in the three arms could bias the result in either direction. Sensitivity analyses reported below model this treatment effect as 15%±7.5% as upper and lower bounds. (In the C/E model described below this efficacy effects enter as 0.85±0.075 times the cumulative probability of progression to a 'severe' disability category of EDSS≥6.)

1.2.2.4 Side Effects

Systemic Flu Like Symptoms--occurs in 52% of patients receiving 8 MIU initially, decreased to 8% at 12 months but remained in 3%-8% of patients through year 5. (IFNB l995) The median time to the first occurrence of flu like symptoms and the median duration per patient was 10.4 days per year (Betaseron® Product Monograph). Many of these symptoms respond to acetaminophen which is not costly. (Piascik l994). Symptoms are decreased by acetaminophen or NSAIDS given before the injection and then repeated every 4 hours as necessary. (Weinstock-Guttman et al, 1995)

Site reactions included primarily pain, pruritis and inflammation. These usually respond to antihistamines and topical corticosteroids. Necrosis occurred rarely (5%) (Betaseron® Product Monograph). One 38 year old woman had severe necrotizing cutaneous reactions following a dose of interferon beta-lb (9 million units subcutaneously on alternate days was reported (Sheremata, 1995)).
Altered laboratory tests-- Only three patients withdrew from the IFNB-lb trial due to abnormal lab results. These were increased liver function tests. (Weinstock-Guttman) Neutropenia, leucopenia, and lymphopenia have also been reported (Betaseron® Product Monograph)

CNS Symptoms--in the IFNB-lb trial in the placebo and 8 MIU groups respectively depressive symptoms occurred in 14.6% and 16.9% in year 1 and 5.1% and ll.1% in year 5 and suicide attempts in 0.0% and 1.6% in year 1 and none in either group in year 2.

Menstrual disorders were significantly greater in patients treated with Betaseron®, occurring in 17% of patients on 8Miu of Betaseron® versus 8 % of placebo.

Other Side effects have been reported in small numbers of patients. Refer to Betaseron® Product monograph for further details.

There is no information on the long term toxicity of Betaseron® after 5 years.

1.3 Generalizability

Patients in the clinical trial were recruited at 12 North American medical centres associated with universities. They had relapsing-remitting MS with at least two acute exacerbations in the two years before entry into the trial, were between the ages of 18 and 50 and had EDSS scores of 5.5 or less. Trial subjects may differ from those in non-trial settings because of centripetal bias (e.g., patients referred to tertiary care centres because of more complications, comorbidity), volunteer bias (e.g., patients enrolled in clinical trials tend to be more motivated, healthy, and compliant) and ease of access (e.g., no financial or geographic barriers to care). However, the mean age at diagnosis of 31, the female to male ratio of 2.5 to 1, and the mean EDSS score at entry of 2.9 for the trial subjects do not differ greatly from similar patients in Nova Scotia. (Brown et al, 1995)

Except for the exclusion of non-ambulatory patients with relapsing-remitting MS, the trial subjects appear to be typical of those with RR MS in other MS populations.

Patients with a benign course were excluded, a relatively small group in which the role of Betaseron® is unknown and unlikely to be tested or administered empirically by clinicians until the role is clarified in more active forms of the disease. The role is also unknown for patients
with relapsing-progressive (RP) and chronic-progressive (CP) disease although trials are underway. Both of these groups are relatively small at onset, comprising about 9% of females and 21% of males in Runmarker and Anderson's well-described Swedish cohort (Runmarker, 1993, p. 117-134). However, the role of such MS disease classifications in assessing lifelong treatments effects, and eligibility for treatment criteria, based on short term RCT data, is problematic. MS classifications assigned patients change systematically from time of onset, where classifications are predominantly relapsing/remitting and benign, to many years (or decades) after onset when classifications independently assigned these same patients are predominantly rp and cp. (Brown et al, 1995)

1.4 From Efficacy to Effectiveness

To what extent can the results of this carefully done clinical trial be transferred to a standard clinical setting? Should the treatment effects be reduced, given the less strict attention to inclusion and exclusion criteria, possibly lower compliance and possibly less effective administration and monitoring of Betaseron \(^7\) in a non-clinical trial setting?

First, with respect to eligibility, it is likely that clinicians will not be so careful in assigning someone to relapsing-remitting and indeed, will be biased towards assigning patients to this class if a payer restricts Betaseron \(^7\) to relapsing-remitting MS only. This will reduce the apparent effectiveness of Betaseron \(^7\) unless it has the same or increased efficacy in another group of MS patients, such as those with chronic progressive disease. Eligibility may therefore be increased while effectiveness is decreased, perhaps to the lower level of the sensitivity analysis reported below.

Second, providers involved in RCTs generally have higher skills and use the interventions more effectively than those in a population setting. This is not likely to be of concern for the use of Betaseron \(^7\) since its use will presumably be restricted to neurologists and its dose and administration fixed for most patients.

Third, patients in clinical trials tend to be healthier and more compliant than those who refuse participation. Participation in the trial at 4.5 years was 45%, and actual compliance with an alternate-day injection of Betaseron \(^7\) is not reported. This rate of 45% is used, in scenarios presented below, as the compliance rate achieved, under RCT conditions, five years after
treatment began. Given the alternate day treatment regimen, side effects, and difficulty in perceiving a clinical effect from the injections, actual compliance at five years may be substantially lower in a general population. As noted in section 1.3, in a study of patients with Parkinson's disease treated with sub-cutaneous morphine, only 20% took the drug for at least two years (Steiger, 1992, p. 389-93). Some scenarios analysed below assume a lower bound in compliance of 20% after five years, with no further reduction in compliance thereafter.

1.5 Effects of Betaseron® Beyond Five Years

Neither lesion number or area as assessed by MRI or exacerbations correlate well with clinical outcome, best measured in this trial by change in EDSS score. Nevertheless, the demonstration that these treatment effects persisted over the five years of Betaseron® treatment suggests that there is an ongoing impact on the pathophysiology of MS. Beyond five years this EDSS effect may 1) persist at the same relative rate, 2) increase or 3) decrease. The reduction in MRI lesions and exacerbation rates experienced during the five years RCT may translate into measurable differences beyond five years in progression of other manifestations of MS of both clinical and economic significance. Whether treatment effects beyond five years will be similar to, larger than, or smaller than the size of treatment effects measured during the five year RCT is, of course, a matter of conjecture at this time.

On the other hand, the RCT increase over time in neutralizing antibodies to Betaseron® may mitigate its long-term effectiveness in some subjects. Given uncertainty regarding efficacy effects beyond 5 years, C/E sensitivity analyses include a scenario where antibody effects in 40% of the treatment group lead to either 1) MS management decisions to discontinue Betaseron® treatment or 2) revisions of treatment eligibility criteria which have the same effect in reducing the number of persons in the MS onset cohort who remain on treatment beyond 5 years.

1.6 Mental Health and Psychosocial Aspects of Betaseron® Treatment

Disturbances in mental health have been considered an important feature of MS with disorders of mood the most commonly discussed mental health problem. Suggested prevalence rates for depression and suicide are reported to be higher for MS patients (Stenager et al. 1992, Schubert and Foliart, 1994) and depression has been reported to precede the onset of neurologic symptoms in a high proportion of MS patients (Whitlock and Siskind, 1980; Sullivan et al., 1995). As
pointed out by Minden and Schiffer (1990) in their review of studies of depression and euphoria in MS, however, many studies suffer from selection bias and a lack of an appropriate comparison group. Other major psychiatric disorders (e.g. psychoses) have less frequently been reported in association with MS (cf. Joffe et al., 1987).

Despite the relatively recent recognition of the importance of mental health issues in MS (cf. Devins and Seland, 1987; Minden and Schiffer, 1990; Murray, 1995), few studies have addressed the issue of mental health service utilization by MS patients. Based on Danish public health records, Stenager and Jensen (1988) reported that 42/366 MS patients (11.5%) required psychiatric hospitalization. A similar rate of psychiatric hospitalization was reported for a small sample by Ron and Logsdail (1989). Pine et al. (1995) found only 10/2720 patients with MS were admitted to two psychiatric facilities over a 10 year period, but they point out that the prevalence of MS in their hospitalized sample was greater than the estimated prevalence of MS in the general population. Minden et al., (1987) reported that although 40/50 patients with MS in their sample had a psychiatric disorder in the past year, only 24 had received any form of treatment and only 16 had received more than 2 weeks of psychotherapy.

Clearly, considerably more information is required regarding the base-rate of depression/depressive symptoms in the population of MS patients and the relation between these symptoms and health care utilization, before the published data on depressive symptoms from the Betaseron® trials can be evaluated within a cost-effectiveness framework. As noted in section 1.1 above, suicide rate data in MS are controversial. In the published Betaseron® data, the low overall rate of suicide attempts and the absence of any attempts in the control group (i.e. 0 base-rate) make interpretation of the suicide data difficult in the absence of clear population-based data for MS patients. Although potentially of greater value in terms of cost-effectiveness modelling, the published data on depressive symptoms are uninterpretable since the source of these data is not described. It would appear from the data presented that depressive symptoms were noted most frequently in the 8 MIU IFNB group but without a description of the manner in which these data were obtained, they cannot be interpreted. The high drop-out rate from the study also begs the question as to whether there existed any relation between the presence of depressive symptoms and subject attrition. The reduction in the reported "frequency of patient-reported depressive symptoms" for the placebo group in years 3, 4 and 5 relative to years 1 and 2 does raise the possibility that subjects in the placebo arm who experienced depressive symptoms were less likely to continue in the study.
Although depression is undoubtedly an important issue in MS, studies of depression have numerous limitations (cf. Murray, 1995) including such issues as the difficulty dissociating symptoms of MS and depression (i.e. fatigue, impaired concentration and memory). Cost-effectiveness modelling of treatment effects in MS must extend beyond simply measuring depressive symptoms and requires broad-based measures of the construct of mental health status which have clear relationships with health care utilization. Nova Scotia's MSID includes data on two such measures: the Sickness Impact Profile (SIP; Bergner et al., 1981) and the Mental Health Inventory (MHI; Veit and Ware, 1983), which were collected for a subset of DMSRU patients (n=193) evaluated in a cross-sectional study conducted from 1989-1992. In previous studies of the general population sample included in the Rand Health Insurance Study, the MHI has been shown to have predictive value for mental health care and general health care utilization and costs (Ware, et al., 1984; Manning and Wells, 1992).

In a compendium of data prepared for the National MS Society of the U.S. by Abt Associates (1993), it is clear that the majority of physician visits by MS patients are because of problematic symptoms (pages 103-105). Although symptoms related to neurologic impairment and mobility restrictions may be addressed adequately by the EDSS, mood disturbance and other prevalent symptoms such as fatigue, pain, bowel and bladder dysfunction, and cognitive impairment, are not. Our own previous work has shown that subjective ratings of fatigue by MS patients are highly correlated with both their general health status and their mental health status (Fisk, et al, 1994). The experience of pain has also been found to be related to mental health status (Archibald, et al, 1994). Thus, more broad-based measures of health status (including mental health) which capture the impact of the diverse MS symptomatology, may have greater predictive value regarding health service utilization. As such, inclusion of more broad-based measures of health status and mental health status will be required in future clinical trials if the full benefits of interventions are to be understood.

1.7 Alternative Treatments

This evaluative study uses MS natural history as the treatment comparator for Betaseron®. The section below reviews literature on other immunosuppressive drugs used to treat the symptoms of MS. None of these alternative treatments were judged to have materially altered the natural history of MS.
The immunosuppressive drugs currently used to treat multiple sclerosis are all controversial. There are few randomized controlled double blind trials with sufficient patient number and of long enough duration to determine efficacy. All drugs have significant toxicities. The next section reviews the potential treatment comparators to Betaseron® and justifies the use of placebo in the economic analysis. Costs of these comparators are provided as hospital or outpatient costs in Nova Scotia in Canadian dollars as of February 1996. Costs of administering the drugs and monitoring therapy are not included. A study of seniors in N.S. showed that few patients over the age of 65 received any of these drugs but their degree of use in other populations in Canada is not published and may be different. (Sketris et al.) The reader is referred to the following references for a comprehensive overview of the treatment options. (Becker et al 1995a, Becker et al 1995b, van Oosten et al 1995)

### 1.7.1 Corticotropin and Corticosteroids

Corticotropin has been used to treat MS since the 1960s and steroids continue to be widely used particularly in the treatment of acute exacerbations. Studies have examined the type of preparation (corticotropin vs corticosteroids), route of administration (oral versus iv) and length of therapy. Several small trials have shown that methylprednisolone increases the rate of recovery from acute exacerbations of MS (Durelli et al 1986, Milligan et al 1987, Warren et al 1986.)

A recent partly blinded study examined the effect of iv methylprednisolone and oral prednisone on the treatment of patients with acute optic neuritis (Beck et al 1992). Patients who received high dose methylprednisolone recovered visual function faster compared to placebo. The patients with isolated optic neuritis may also have a delayed onset of MS, with the adjusted rate ratio for developing definite MS 0.34 (95% CI 0.16 - 0.74) as compared to placebo.

Low or moderate doses of corticosteroids alone have not been shown to have significant benefit in progressive MS (Bansil et al 1995).

The adverse effects of corticosteroids are many including weight gain, alterations in mood, hirsutism, hyperglycaemic, osteoporosis, myopathy, electrolyte disturbances and hypertension.
The cost of ACTH used by Rose et al 1970 (40 units twice daily for 7 days, 40 units once daily for 4 days and 20 units daily for three days) using a cost of $12.25/40 unit vial is $245/year. The cost of IV methylprednisolone used by Beck et al 1992 (250mg every six hours for 3 days followed by 11 days or oral prednisone 1 mg/kg/day assuming a 70 kg person) is $213 ($8.83/125 mg vial of methylprednisolone sodium succinate and $0.07/50 mg tablet prednisone).

### 1.7.2 Azathioprine

Azathioprine has been used in the treatment of MS primarily in noncomparative, or unblinded trials since the 1970s. (Becker et al 1995a). Some double blind trials in small numbers of patients have shown favourable results for azathioprine (Merten et al 1982, Goodkin et al 1991), while others have not (Ellison et al 1989,British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988) A meta-analysis conducted by Yudkin et al 1991 showed that after two years azathioprine-treated patients had small decreases in disability as measured by EDSS. The benefit is seen after 2 years of therapy so patients who are rapidly progressing are unlikely to benefit.

Side effects usually include decreased red and white blood cell counts which are often managed by dosage reductions. Increased susceptibility to infections, hepatotoxicity, nausea, vomiting, fever and rash may also occur. There is a theoretical increased rate of cancer, but one study suggested this risk was minimal (Amato et al 1993).

The cost of azathioprine (dose of 2 mg/kg/day for 70 kg) for 12 months is $941.

### 1.7.3 Cyclophosphamide

Cyclophosphamide has also been used in the treatment of multiple sclerosis since the 1970's in many nonrandomized nonblinded trials with no effect or some clinical improvement. (Hommes et al 1980, Becker et al, 1995b). Two large randomized single blind trials have been performed. A Canadian trial of 168 patients with MS was conducted. The patients were assigned to one of three treatment groups (1) Cyclophosphamide 1000 mg IV every other day adjusted to white blood cell count with maintenance prednisone treatment, (2) Cyclophosphamide 1.5-2 mg/kg/day orally plus alternate-day prednisone plus a plasma exchange or (3) oral placebo plus sham plasma exchanges. There was no difference in worsening of MS which was defined as a two step change in the EDSS score. There are many commentaries about his trial and
explanations for the reasons for which no treatment effect was seen including the possible release of corticosteroids by the sham plasma exchanges (Mitchell et al 1993)

The Northeast Cooperative Multiple Sclerosis Treatment Group study was a single-blind randomized non-placebo controlled trial of 256 patients with chronic progressive MS who received two different induction regimens of Cyclophosphamide. One was standard corticotropin for 21 days and Cyclophosphamide 400-500 mg/day iv for 10-14 days and the other was Cyclophosphamide 600 mg/sq m iv on days 1, 2, 3, 6, and 8 plus im corticotropin. After induction half of the patients received a maintenance regimen of Cyclophosphamide (700mg/sq m2 iv every two months for two years). Maintenance therapy slowed disease progression at 24 months with younger patients particularly benefiting. Various limitations in this trial have been noted. (Becker et al 1995b)

Cyclophosphamide has many adverse effects the most common severe adverse effect being leukopenia. Alopecia, severe nausea and vomiting, haemorrhagic cystitis, amenorrhea, pulmonary fibrosis and malignancies also may occur (Mitchell 1993, Becker et al 1995b).

The Cyclophosphamide regimen costed is 700 mg/m2 iv every 2 months for 12 months. If a dose of 1000 mg is assumed ( $8.70/1000 mg vial) the cost would be $52/ year. As many patients are hospitalized to receive iv cyclophosphamide, the costs of this treatment would need to be added. The cost of 2 mg/kg of oral Cyclophosphamide for 12 months (assume three 50 mg tablets/day of Procytox at $0.56/tablet and a 2% markup and a $9 dispensing fee) would be $60/month or $ 725/year.

1.7.4 Cyclosporin

Cyclosporin has been used in a number of trials. The largest was a double blinded placebo controlled trial called the Multiple Sclerosis Study Group trial. This involved 547 patients with chronic progressive MS who were randomized to cyclosporin 6 mg/kg/day orally or placebo for 24 months. The trial showed a modest decrease in the EDSS score (0.39 ± 1.07 than the placebo group 0.65 ± 1.08) at 24 months.

Adverse effects of cyclosporine include nephrotoxicity, hypertension, hyperkalemia, increased susceptibility to infections and malignancies.
The cost of cyclosporin 6 mg/kg/day for 12 months for a 70 kg person is $8621.

1.7.5 Other marketed agents

Small trials of the use of mitoxantrone, methotrexate and intravenous immune globulin have also been conducted but these agents are not widely used. A number of drugs are in controlled trials eg copolymer-1, cladribine, interferon beta 1a, alpha interferon. (Becker et al 1995a, Becker et al 1995b, Van Oostern et al 1995). In addition, plasma exchange has been used.

This review of other immunosuppressive drugs used in MS concludes that none serve as a direct comparator for Betaseron® treatment in modifying MS natural history, however useful they may be in relieving various MS symptoms.

1.8 Pharmacoepidemiology/Pharmacoeconomic Aspects of Betaseron®

Many drugs have been used (eg azathioprine, cyclophosphamide, cyclosporine, methotrexate, sulfasalazine, methylprednisone), or are being investigated in an attempt to alter the disease course of MS (eg alpha interferon, interferon beta-1b, interferon beta-1a, copolymer-1, cladribine, immune globulins, fampridine or antibodies to CD4 cells.) (Becker et al 1995 a, Becker et al 1995b, Bates 1995, Connelly 1994, Goodkin 1994, Goodkin et al 1995, Kelly 1994, Noseworthy 1991, Rudnick 1994). Because of the limited success of previously marketed drugs, placebo was chosen as the treatment comparator for Betaseron® and this was used in our analysis. Future studies may attempt some combination of therapy, and practice patterns may show some combination of therapies, but we did not investigate these.

Because of the low prevalence of the disease, there are few population based studies regarding drug utilization. We found using administrative claims databases from the Nova Scotia MSI Pharmacare program for persons age 65 and over who had attended the Dalhousie Multiple Sclerosis Research Unit that MSI Pharmacare costs in 1993/1994 for persons with MS (N=52) were $973 per capita compared to $590 per capita (61% greater) for all seniors in NS (N=108,646). Specifically they received alpha blockers, anticholinergics, cholinergic, tricyclic antidepressants, anticonvulsants, drugs combatting fatigue, antispasticity agents, and antibiotics for bladder infections more frequently than other seniors. (Skefris et al 1996)
There are few postmarketing data on compliance with Betaseron® in patients who are not in clinical trials. Compliance for other drugs which are injected subcutaneously (eg insulin, desferoxamine, sumatriptan, salmon calcitonin, erythropoietin, apomorphine, heparin) varies (McCaul et al 1987, Diehl et al 1985, Bertovitch et al 1995, Bougneres et al 1993). In a study of patients with Parkinson's disease treated with subcutaneous apomorphine after 2 years only 20% were taking the drug (Steiser 1992). Approximately 50% of patients are noncompliant for all types of medications. (Coambs et al, 1995) The US postmarketing data has shown that approximately 20% of patients discontinue Betaseron® during the first 12 months (correspondence Jean-Francois Grenier, Berlex Canada, Jan 10, 1996),

The decision to take the drug after it has been prescribed or to refuse treatment is based on a number of factors but includes the patient's health belief model. While this has been studied for other disease conditions such as, eg hypertension, there is little information on MS. It is highly unlikely that all eligible patients will choose to be treated.

1.9 Discussion

After many decades of disappointing studies of agents that might alter the underlying disorder in MS, virtually all these therapies have been discarded because of lack of reproducible and clinically significant benefit. The accepted therapy for the disease was high dose steroids intravenously for acute attacks and an array of symptomatic treatments for the effects of the disease. No treatment had been found which altered the underlying disease process and to alter the eventual progression of the disease. The attention given to Betaseron® is thus understandable and important as a step forward in the search for a more complete answer to a disorder that affects a large number of young and middle aged adults (a combination of clinical and administrative data indicate a prevalence of 297 per 100,000 in Nova Scotia, 36% higher than predicted by local experts). (Brown et al, 1996)

Since Charcot's clinical description of the disorder in 1868, it has been recognized that the disease was a progressive one, sometimes slowly progressing, but often occurring in attacks with eventual accumulation of neurological disability. Pathology showed that there were demyelinating lesions throughout the central nervous system in these patients, and clinically it was inferred that a lesion developed when symptoms developed. With the advent of the MRI,
we learned that lesions occurred in a much more scattered pattern, often occurring when there were no new symptoms, and it was difficult to associate specific lesions and symptoms. The concept of "burden of illness" on the MRI was a measure of the number and area involved by visualized lesions. Although it is difficult to demonstrate high correlation of MRI lesions with clinical disability in individual patients, recent studies suggest there is a general correlation of increasing MRI burden of illness with progressing disability. (Vanderveen et al, 1995) Also, patients who have repeated attacks of new symptoms (exacerbations) show evidence of increasing neurological involvement, suggesting an accumulation of damage (demyelination and gliosis) over time.

Clinical experience would suggest that a reduction in acute exacerbations, a reduction in the severity of acute exacerbations and a decrease in burden of illness (using lesion numbers and size on the MRI as a surrogate outcome measures), would have a positive effect on the rate of progression and the extent of disability and impairment in the long term. (Walderveen et al, 1995) Such an alteration of the attacks and disability would also reduce physician visits, hospitalizations, and the use of medications to treat acute attacks and to manage symptoms of the disease. In the case of Betaseron®, the effect was moderate (up to one third reduction, 24% to 33%) in the case of acute attacks, which may reduce use of MS-related health services by a similar proportion in practice. Another important observation was that the reduction in exacerbations was just as great in the fifth year as it was in the first, although the reliability of the estimate for this year is much lower because of decreasing exacerbations over the course of MS and the smaller number of subjects remaining in the trial.

Although the IFNB study had insufficient power to detect a clinically important reduction in long term disability, and clinical trials to show effects beyond five years have not been conducted, it is reasonable to surmise that the eventual outcome in the disease should be altered. For instance, in the initial three-year report of this trial of relapsing-remitting MS patients, 72% of the placebo group had not yet met the criteria for progression, i.e., a 1 unit increase in EDSS score confirmed at another clinical assessment at least 3 months later. By a median duration of 46 months, however a difference was beginning to show, with 46% of the placebo group showing progression, compared to 35% in the 8 MIU group. The IFNB study listed 4 reasons why they failed to show a significant effect on disability, but a fifth may be more important - they studied only relapsing-remitting cases, a type of MS that often shows less progression in the early years. This can be seen in the placebo group, who also showed little progression. It would be difficult to demonstrate progression in the years when little progression is expected.
The greatest interest about Betaseron® to neurologists was not the decrease in acute attacks but the promise provided by the very significant reduction in the MRI evidence of new lesions. This *may indicate* that the underlying process in the disease was being suppressed. "While there is no conclusive evidence linking changes in MRI lesion load with changes in health status the evidence in favour of this link is growing." (Metz, 1995)

A negative shadow over this promise was cast by the appearance of neutralizing antibodies to Betaseron®, and the early evidence that the presence of such antibodies may mean a decrease in effectiveness of the therapy over time. How many cases may eventually develop neutralizing antibodies, and whether this means the effectiveness will eventually fade in many or most cases remains to be seen. Further analysis of the patients with and without neutralizing antibodies is expected from the investigators soon.¹ It will be of interest to see if the patients in the treatment arm who were showing progression were more often showing the presence of neutralizing antibodies. It would also be important to see the rate of development of antibodies over the years of the study and beyond. US and Canadian guidelines regarding appropriate treatment suggest not using Betaseron® if antibodies develop. (Oger, 1995) A note of caution respecting antibodies is raised in correspondence from Jean-Francois Grenier, Berlex Canada, Jan 10, 1996, which reports the puzzling phenomena that similar antibodies developed in some patients in the placebo arm of the Betaseron® RCT.

In considering the early side effects and adverse reactions, the drug is well tolerated over the long term. Many of the side effects occur in the first months of the treatment only. It is difficult to assess the depression and suicide data presented since the measurement of depressions was not well-described and suicides were rare. Depression is well recognized as a feature in many MS patients and occurred at similar rates among the three groups. It should be mentioned that being a subject in a clinical trial can be disheartening for some - they are in a trial, but often regard it as getting "the new treatment", and may drop out when they find they are worsening or having attacks, or suspect they are on a placebo. On the other hand, the suicide data is also problematic. The BC group has previously reported a significant suicide rate in their MS patients, an

¹ Because of the improved sensitivity of the new assay of 1,725 samples (placebo 927 and 8 MIU 798) analysed as of Dec 1995, only 21% of samples tested positive. (Correspondence Jean-Francois Grenier, Berlex Canada, Jan 10, 1996).
experience not shared by many other MS clinics. In short, the depression and suicide data to date does not alter the calculation of overall benefit of this therapy.

The authors of the IFNB study cautiously concluded that there will be uncertainty about the role of Betaseron® in the treatment of MS but felt there was evidence that it would be useful to reduce attacks of MS and likely would reduce disability in the long term.

Reasonable conclusions for a clinician would be:

1. Betaseron® is the first drug released which has been shown to alter the underlying demyelinating process in MS
2. It is well tolerated with few long term serious side effects
3. It reduces the number of acute exacerbations of MS which should reduce the need for physician care, hospitalizations and drugs.
4. The number and area of lesions in the central nervous system (CNS) as determined by MRI are reduced which would suggest the underlying disease activity is reduced.
5. These effects on the disease would be expected to eventually reduce the disability and the rate of progression in the disease over time, even though studies do not exist which show this.
6. Since the underlying process seems to be altered by Betaseron®, it should have benefit in other forms of MS, such as chronic progressive and relapsing-progressive, which haven't yet been fully studied (although the studies are in progress).2
7. These promising findings are mitigated in part by the development of antibodies is in a sizable minority of treated patients by the end of the five year trial.

1.10 Therapeutic Assessment Summary

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2This has implications for who will be offered therapy with Betaseron®. Only one group was studied, and it was the group easiest to measure changes in, the relapsing-remitting type. If the underlying process is slowed by the therapy with Betaseron®, it should also benefit the other groups of MS patients, even though they have not yet been studied. Decision makers may wish to limit an expensive therapy to the relapsing-remitting cases as they were the only ones to be shown to benefit. It will be hard for clinicians to withhold therapy from the most tragic of MS patients, the very progressive cases, just because we have not studied them.
(1) There was a 24% - 33% reduction of exacerbation rate in the 8 MIU group. Although exacerbation rates decreased over the study period in both placebo and treatment groups, the reduction by 24% - 33% in the treatment group persisted into year 5.

(2) There was a significant reduction of new lesions on the MRI in the 8 MIU group over placebo, in that the treatment group showed no significant progression of new burden of illness, while the placebo group had a highly significant increase in lesion area.

(3) Neutralizing antibodies were detectable in 38% of patients by the third year and were associated with a significant attenuation of treatment effect on exacerbation rate.

(4) In those without detectable neutralizing antibodies the reduction of exacerbations was 50%.

(5) The burden of illness as measured by the MRI correlated with the degree of disability, and an increase in the burden of illness in the study also correlated with an increase in disability.

(6) Confirmed progression of the disease by one EDSS point, measured by Kaplan-Meier curves, occurred in 35% of the 8 MIU group compared to 46% in the placebo group (p=0.096), with rate of disability progression being reduced by up to 15%.

(7) The study neither established nor ruled out an effect of IFNB in limiting progression of disability but the study was not originally designed with sufficient power to show a treatment effect on disease progression.

(8) The long term side effects of Betaseron® were minimal.
II THERAPEUTIC AND ECONOMIC ASSESSMENTS IN CHRONIC PROGRESSIVE DISEASE

2.1 Therapeutic Assessment Challenges

The therapeutic assessment challenge is to measure treatment-related changes in health-related-quality-of-life (HRQoL), experienced over various health status dimensions, and to fairly represent their collective impact on HRQoL expected over the natural history of MS, using quantitative and qualitative evaluation methods. This challenge is complicated by various factors, including the inherent complexity and variability of MS progression and our limited capacity to measure changes in health status sensitively.

This analysis uses a conceptual evaluation framework for multiple sclerosis outlined by Alan Williams (Williams, 1990), which adapts standard economic evaluation methods applied to health services and health technologies. The evaluation models the natural history of multiple sclerosis from time of onset to death, in terms of “health related quality-of-life”. HRQoL is depicted as an index number, constructed using relative-value weights, mapped on a scale from 1.0 to 0.0, where 1.0 represents normal health and 0.0 represents death.

A stylized MS natural history time path (NH) is plotted against HRQoL in Figure 1. The NH starts from a healthy state, with a high HRQoL, at time of onset of MS symptoms, and gradually progresses to lower and lower levels of HRQoL until time of death. For PwMS classified as having “relapsing-remitting MS”, progression is also characterized by random episodes of acute exacerbations followed by remissions. This is represented in Figure 1 as a downward spike in the NH path, followed by a recovery to the long run NH trend. (Williams, 1990)

This NH framework focuses on treatment effects which manifest themselves as improvements in HRQoL rather than greater length of life. Length of life from time of onset of MS symptoms is typically long, given that onset usually occurs before age 35 and that life expectancy for PwMS is not much lower than that of the population at large. In Figure 1, length of life subsequent to onset of MS symptoms is shown as 40 years.
Figure 1: Modelling Treatment Effects on Multiple Sclerosis Progression

NH=MS Natural History Path; E1=MS Path given treatment having efficiency E1
The stylized natural history path (NH) in Figure 1, while an over-simplification of the complexity and diversity of MS progression for an individual person with MS, captures two essential features of this chronic progressive disease. The first is the systematic element of MS disease progression which over time contributes to a gradual decline of HRQoL. The second is the random element in MS progression which manifests itself from the time of onset to death.

The upper time path (E1) in Figure 1 represents treatment effects that slow the rate of MS progression. Slower MS progression may be manifested, for example, by delay in the onset of more severe symptoms, disabilities and handicaps. Treatment effects may also delay the onset of exacerbations and reduce their frequency and severity, illustrated by a more moderate pattern of exacerbation/remissions relative to those shown for the NH path.

Treatment effects which slow MS progression and/or reduce exacerbations will improve HRQoL relative to the NH. Improving HRQoL also increases total Quality-Adjusted-Life-Years (QALYs). QALYs are the sum of years lived, weighted by the HRQoL experienced in each year. Holding the number of years lived constant, improving HRQoL, increases QALYs.

In Figure 1, QALYs are represented by the area below the time path. If HRQoL remained ‘perfect’ (with value 1.0) from time of MS onset to death, total HRQoL-weighted-years, or QALYs, would be represented by area “abcd” (40 years x 1.0). QALYs experienced over the natural history of MS are represented by the area under NH (the area “abd”). The area above the natural history path (the area “bcd”) represents potential QALYs lost due to MS. Treatment effects which shift the MS progression path from NH to E1 increase QALYs by the area between NH and E1. Total QALYs are now represented by the area under E1.

The natural history and treatment time paths of individuals are randomly distributed about the stylized NH history path in Figure 1. In the analysis of Betaseron® C/E, the MS natural history path used comes from an MS-onset-cohort followed prospectively for 25 years, while treatment effects are estimated using short run RCT efficacy results and other data, e.g., compliance rates and antibody formation rates. In Figure 1, treatment path E1 is depicted as rightward shift of the MS natural history path which is roughly proportional to time since onset of symptoms and time since treatment began. This particular depiction of the shift from NH to E1 takes into account the wide age distribution (up to age 50) and years since onset distribution of PwMS recruited into the
Betaseron® RCT, together with RCT evidence on treatment size effects which appears to be unrelated to age or years since onset.

The area between the NH path and the E1 path, on a figure drawn to scale, shows the magnitude of QALYs gained from treatment effects which slow MS disability progression. An evidence based E1 will reflect the short run treatment effects on the rate of MS progression, as measured by HRQoL, up to but not beyond the duration of the RCT.

For purposes of analysing treatment effects over the long natural history of MS it is necessary to make assumptions about the nature and size of treatment effects beyond the time frames reported in RCTs. There are essentially three options. The first is to assume that the nature and size of treatment effects found in RCTs continue indefinitely, in which case the E1 path depicts both short and long run treatment effects. The second option is to assume that treatment effects experienced over the short run gradually erode over longer periods of treatment. In this case, the long run treatment path will fall between the NH path and the short run treatment path E1. The third option is to assume that long run treatment effects are greater than short run effects, in which case the long run progression path lies above E1.  

Modelling MS natural history as the comparator for specific therapeutic interventions is subject to limited availability of long run data on MS progression. The data that is available is not necessarily ideal for measuring treatment outcomes which reflect HRQoL. RCT evidence on treatment effects is necessarily short, relative to MS natural history, which necessitates bold assumptions in assessing therapeutic effects beyond the short time-frames of most RCTs. Beyond the foregoing challenges associated with measuring treatment effects in MS, construction of a HRQoL health index requires information on the relative values which PwMS place on incremental gains in each of the various health status dimensions impacted by MS progression.

Estimating the health consequences of therapies designed to delay MS progression, using a HRQoL index, involves all of the foregoing methodological challenges and empirical

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3 While analysts and policy makers may both feel uncomfortable in having to make assumptions about long run effects, they may take some solace in the fact that present-value calculations (literally) discount the health outcome consequences of long term assumptions relative to the health outcome consequences based on short-run evidence-based results.
constraints. Where an MS therapy is prescribed on a continuous and long term basis, from time of onset (or definite diagnosis of MS) until death, or some other endpoint prior to death, it is appropriate to analyse these therapeutic consequences over this long natural history of MS. The therapeutic assessment challenge, as illustrated in Figure 1, is to estimate treatment-related “health-related quality-of-life years gained,” QALYs. Graphically, QALYs are measured by the area between the NH and E1 progression paths. This estimate of treatment-related QALYs gained over the natural history of MS enters as the denominator in a Cost / Utility (C/U) or a Cost / Effectiveness (C/E) analysis.

2.2 Economic Assessment Challenges

The evaluation challenges faced on the economic assessment side of cost/utility (C/U) or cost/effectiveness (C/E) evaluations appear modest in comparison to the therapeutic assessment challenges reviewed above.

The economist's role is to place the net health benefits gained as a consequence of treatment X against the net economic costs associated with treatment X. The resulting C/U or C/E ratios estimate the cost per unit of health benefit gained. Where a C/U analysis is undertaken, the estimate will be cost per quality-adjusted-life-year (QALY) gained, where all years analysed are quality-adjusted using a particular generic health-related quality-of-life (HRQoL) index. Where a C/E analysis is undertaken, with health outcomes (E) measured in natural units (e.g., disability day lost per year) rather than transformed into a HRQoL index, the estimate will be cost per health outcome measurement unit gained (E).

C/U estimates are preferable to C/E estimates because C/U estimates based on generic HRQoL indices are, in principle, comparable across all disease states and therapeutic interventions, whereas C/E estimate comparisons are restricted to other (usually disease specific) studies which have reported similar effectiveness measures. C/U estimates are in principle more useful for informing policy decisions about health resources allocations in general, across all disease states and interventions. C/E estimates also inform policy decisions, but only for a more restricted set of disease states and interventions.

C/U or C/E estimates in themselves do not tell policy makers whether it is worthwhile to fund a particular therapy or program. C/U and C/E estimates, being ratios of costs relative to health
benefits, measure only relative cost/utility and cost/effectiveness, which is of limited usefulness in and of itself. Such measures become more useful when they can be compared and rank-ordered relative to similar estimates reported in the scientific literature. But even the relative ranking of a C/U ratio will not, by itself, indicate whether a therapy should be funded. In deciding whether or not to recommend a new therapy for funding, decision-makers must take into account their particular budget constraints, their own appreciation of the relative worth of the therapy in question, and the strength of evidence brought to bear.

For comparative purposes it is desirable to have as much standardization as possible for both health outcomes and costs. In practice there is great diversity in measuring and reporting both health outcomes and costs. This diversity reflects different judgements concerning which measurement instruments are appropriate for a particular evaluation, the historical evolution of measurement instruments, and practical constraints such as availability of data, research funds and time constraints. There is at present no “gold standard” concerning health outcome measurement instrument, although there appears to be growing consensus about what should be measured in principle. On the cost side, there is recognition of the various layers of costs which should be included in an complete analysis, but great diversity in practice regarding what is actually included and to at what level of precision. The absence of standardization across C/E and C/U studies of health services and technologies means that decision-makers, and other end-users of these studies, must exercise caution in interpreting and making comparisons across these studies. Decision-makers may not have a difficult job at the extremes, where there is either a very low C/U or a very high C/E ratio reported in a study, but may find it quite difficult to make fine judgements when C/U or C/E ratios fall in an intermediate range.

This therapeutic and economic evaluation of Betaseron® in MS includes a cost/effectiveness analysis in which health outcomes are measured using a (normalized) EDSS (categorical) disability score (nEDSS). Cost/efficacy analysis may be regarded as a special case of cost/effectiveness analysis, where effectiveness is modelled as equivalent to efficacy results achieved under RCT conditions.

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* A recent compilation and rank-ordering of such studies is provided by Tengs TO, Adams ME, Pliskin JS, Safran DG, Siegel JE, Weinstein MC, Graham JD (1995), "Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness," *Risk Analysis*, 15(3): 369-90. These studies are comparable by virtue of using a common effectiveness measure, i.e., a year of life saved (or a premature year of death avoided). See Appendix D for excerpts."
A cost/effectiveness spreadsheet model is developed. Estimates of program costs for Betaseron® treatment in MS, and cost/effectiveness ratios, are analyzed for various scenarios. The Betaseron® treatment effect measured by a slower rate of EDSS disability progression represents but one of several important treatment effects measured in different domains of broadly conceived health status indices. Following presentation of C/E results based solely on normalized-weighted disability-years-avoided (nEDSS-DYA) consideration is given to relationships between MS progression, as measured by EDSS progression, and MS progression and consequences as measured by various other instruments. Time and budget limitations precluded extension of Dalhousie's C/E spreadsheet model to a full-spectrum analysis of treatment outcomes important to persons with MS. Through qualitative discussion of strengths and limitations of C/E results based on EDSS disability outcomes, however, the research team hopes to provide a balanced assessment of Betaseron®'s therapeutic and economic consequences.

2.3 Cost/Utility and Cost/Effectiveness Evaluation Framework

Therapeutic assessments and economic assessments are jointly undertaken in the cost/utility and cost/effectiveness evaluation frameworks adopted for this study. The natural history of MS is adopted as the appropriate time frame to use in analysing MS with its characteristic early age of onset and near normal life expectancy.

Full economic evaluations include both net treatment (program) costs and net treatment consequences (outcomes) for two or more alternatives. In this MS study, Betaseron® treatment outcomes are compared to MS natural history outcomes. MS natural history is used as the comparator because no treatments prior to Betaseron® have successfully altered the MS natural history progression, though various treatments alleviate MS symptoms.

A Cost / effectiveness (C/E) ratio may be written as:

\[ C = \frac{\text{net treatment costs}}{\text{net health benefits}} = \frac{\text{treatment costs} - \text{costs foregone}}{\text{HS(t)} - \text{HS(nt)}} \]

C represents net (incremental) treatment costs, comprised of Betaseron® direct treatment costs less health care costs foregone, and E represents net health benefits from efficacious treatment.
which raises health status (HS) from HS(nt), health status given no treatment, to HS(t), health status given treatment.

The natural history of MS is adopted as the appropriate time frame for analysing Betaseron® treatment effects on MS progression, given early age of MS onset and near normal life expectancy. Over a long 40 year natural history of MS, treatment effects are summarized by measures which weight each year subsequent to onset of MS symptoms by the disability experienced in that year. In analysing Betaseron®, using nEDSS to represent MS disease progression, the summary C/E measure reported is $C/E_{nEDSS-DYA}$, or cost per normalized EDSS-weighted Disability-Year-Avoided over the natural history of MS.

2.4 Analyses Undertaken

The therapeutic and economic evaluations of Betaseron® undertaken in this report are based on treatment effects reported in the IFNB five-year RCT, on data which place such treatment effects in the context of MS natural history progression, on data which describe how costs increase with MS progression, and on direct treatment costs for Betaseron®. The nature of data available from the first three sources of data determined the types of analyses undertaken.

Three types of analyses were undertaken. Estimates of C/E ratios for Betaseron® treatments affects which reduce the frequency, duration and severity of exacerbation episodes are dealt with briefly in section 2.5 below. $C/E_{nEDSS-DYA}$ estimates for Betaseron® treatment effects which slow the progression of MS disability are dealt with extensively in Chapter III. An exploratory analysis dealing with the relationship between $C/E_{nEDSS-DYA}$ estimates for Betaseron® in slowing disability progression and $C/U_{GENERIC-QALY}$ estimates is found in Chapter IV, section 4.5.

2.5 C/E Ratios for a Reduced Exacerbation Rate Treatment Effect

Analysis of the cost/effectiveness of Betaseron®’s first treatment effect, a reduced exacerbation rate for PwMS classified as relapsing/remitting, concluded that the cost of avoiding an exacerbation episode was quite high. Although a 24%-33% reduction in exacerbation rates was achieved this is equivalent to about one fewer exacerbation episode over three years. (In the IFNB trial the exacerbation rate in the placebo group at the end of two years was
Given direct Betaseron® treatment costs of $16,685 per PwMS per year, the cost per exacerbation episode avoided over three years $48,804 in drug costs alone. The direct health care costs avoided given one fewer exacerbation episode annually are modest. In Nova Scotia, outpatient clinic care per episode costs about $422 (GP $27, Consultant $90, IV methypredisolone drugs $125, clinic costs $30, nursing $150). Most steroid treatment should be done on an outpatient basis but some hospitalizations might occur.

The investigators were unable to find data which would permit documentation of actual health care costs per exacerbation episode. Dalhousie University’s Multiple Sclerosis Integrated Database (MSID) contains both MS clinical data and public sector health care cost data, but the clinical visit data per PwMS were not sufficiently frequent, complete and detailed to enable identification of all exacerbation / remission episodes. Identification of all exacerbation episodes is required to determine actual health care costs per exacerbation / remission episode. However, MSID patient records which included both clinical data and Nova Scotia Department of Health data were used to document total Medicare Costs of PwMS in Nova Scotia. These total cost data provide an upper bound to costs related to exacerbations.

Annual costs of direct health care for PwMS are high relative to persons of similar age and sex in the general population (Brown, 1996). However the absolute annual cost per PwMS is small compared to the direct cost of Betaseron® treatment per PwMS per year. For example, annual costs per PwMS in the DMSRU study group for all physician services was about $400, hospital inpatient and day surgery services were about $2700 (priced at $500/day), and Senior’s Pharmacare Program benefits for PwMS age 65 or more were about $900. Total Medicare costs (physician services, hospital and diagnostic services, and Senior's Pharmacare benefits) averaged less than $4,000 per PwMS in Nova Scotia in 1992-93.

Costs were substantially higher for the 26% of PwMS who were hospitalized during the year, and correspondingly lower for the 74% not hospitalized. Costs rise gradually over the natural history of MS, from relatively low health care costs in the years immediately following onset of MS symptoms (when exacerbation rates are highest) to relatively high health care costs in later decades (when MS-related disability are highest).

Exacerbations likely account for a minority of hospital days by PwMS. Diagnostic code data on hospital admission/separation records for PwMS in Nova Scotia show MS as the primary diagnosis for separations involving 30% of annual hospital days, MS as one of (up to five)
secondary diagnostic codes for separations involving 48% of annual hospital days, and “other” diagnoses for separations involving the remaining 22% of annual hospital days. If hospitalizations for purposes of treating exacerbations are likely to be recorded as a primary diagnosis, the admission / separation diagnostic data suggest that at most about one quarter of hospital costs by PwMS are related to exacerbations. A quarter of $2700 annual hospital costs is $675, which is likely an overestimate of the annual hospital costs by PwMS attributable to exacerbations.

The foregoing suggests that total health care costs associated with MS exacerbations are less than $1,500 per PwMS per year in Nova Scotia, assuming that hospitalizations related to exacerbations are much more frequent than is necessary. A reduction in exacerbation rate of 24% - 33% may avoid about $300 - $400 of health care costs annually. By comparison, Betaseron® direct treatment costs per PwMS per year are $16,685, exclusive of supplementary incremental costs associated with treatment. Supplementary costs, which include syringes (a patient expense which is estimated to cost about $200 annually), additional physician visits to monitor tolerance and to treat side effects, and additional laboratory tests recommended to monitor long term effects, will likely add less than 1% to direct treatment costs. However, if physician practice patterns evolve so that PwMS on Betaseron® treatment were monitored annually by MRI and by batteries of expensive laboratory tests then supplementary treatment costs might exceed 1% or direct treatment costs.

Data on costs associated with exacerbations, other than direct health care costs, have not been determined. Indirect costs due to lost productivity from disability-days lost at work and in the home are likely the most important costs other than direct health care costs.

Estimates of QALYs gained due to a reduced exacerbation rate have not been made. Given the small number of exacerbation-days avoided annually (i.e., less than 30), the cost per QALY gained due to a 24% - 33% reduction in exacerbation rate appears to be relatively high.
III COST/EFFECTIVENESS OF BETASERON® IN SLOWING PROGRESSION OF MS DISABILITY, FROM A DEPARTMENT OF HEALTH PERSPECTIVE

3.1 Introduction

More analytic effort is spent evaluating Betaseron®’s second treatment effect, a reduced rate of MS disability progression, than was spent on Betaseron®’s first treatment effect, a reduced frequency, duration and severity of acute exacerbations. Why is greater attention given to the reduced disability progression treatment effect than to the reduced exacerbation rate treatment effect, given that statistical evidence in support of the former effect is weaker than that for the latter effect? The greater attention given to reduced disability progression is considered warranted because the potential health outcome consequences and resource utilization consequences of even a modest (15%) reduction in disability progression, over the long natural history of MS, are potentially much greater than those from a larger (24%-33%) reduction in exacerbation rates. (McCloskey 1996)

The typically relentless progression of MS to ever higher levels of physical disability, with corresponding increases in the frequency and severity of various MS symptoms, is accompanied by both a gradual erosion of HRQoL and by increased resource utilization and dependence, particularly by PwMS with severe disabilities. By comparison, the magnitude of potential improvements in HRQoL and reductions in resource utilization associated with reductions in the frequency and severity of exacerbation rates - which are relatively infrequent (1.27/ yr), of short duration, and which decline in frequency and severity with time since onset - appear more modest.

A priori, favourable C/E and C/U ratios are more likely to emerge from treatment effects which operate on the broader range of MS health consequences over the long run, rather than from a treatment effect which impacts on the frequency and severity of transitory exacerbation rates over a shorter time horizon.
3.2 Neurological and Physical Disability Progression Over MS Natural History

The rate of progression of MS-related disability is measured in the Betaseron® clinical trial using the (Kurtzke) Extended Disability Status Scale (EDSS). (Kurtzke 1955, 1983)\(^5\) The time elapsed from entry in the trial to progression by one point on the EDSS scale was measured during the five years trial. Differences in time to progression by one EDSS point in the treatment and placebo groups were analysed using Kaplan-Meier survival curves. The rate of disability progression was slower in the 8MIU treatment group than in the placebo group, but the statistical difference was marginally significant at the 10% confidence level.

Use of the EDSS as the primary measure of progression of MS-related disabilities is subject to various criticisms. The prominence given to difficulties of ambulation in the EDSS, while largely ignoring other important dimensions of MS-related and of general health status, makes the EDSS less than ideal for purposes of measuring health outcomes in a comprehensive way. There are now many generic health status indices which are better suited than the EDSS as health outcome measures.

Despite its weakness the EDSS progression is used as an endpoint in virtually all trials of beta interferon therapy in MS. Presumably the long history and worldwide use of the EDSS serves to connect RCT treatment effects on rate of MS progression, measured using the EDSS, to existing clinical data and literature on MS progression which includes EDSS assessments.

Originally developed as a categorical scale describing stages of MS-related neurological symptoms, disabilities and progression, it remains useful in roughly ranking PwMS by severity of MS-related disabilities, and particularly those related to mobility, from very mild to severe up

\(^5\) A copy of the EDSS instrument is in Appendix 1 at the end of this chapter. The EDSS is scored from 0 to 10 using ½ point steps. Scores are defined in terms of Physical Manifestations (ambulation, activity limitations such as ability to work a full day, aids to ambulation, bedridden, and self-care capabilities) and Functional System scores (pyramidal, cerebellar, brainstem, sensory, bowel & bladder, visual (optic), mental (cerebral) and other) which measure severity of neurologic impairment. Assignment of EDSS scores involves clinical judgement. EDSS scores from 0 - 5.5 refer to PwMS who are fully ambulatory without aids (cane, crutch, brace), but who may have limited mobility and stamina. EDSS scores of 6.0 - 6.5 indicate that aids to ambulation are required and mobility is limited to less than 100 metres without resting. EDSS 7.0 - 7.5 scores indicate restriction to a self-propelled of electric wheelchair. EDSS scores from 8.0 - 9.5 indicate that the PwMS is bedridden, with increasing degrees of helplessness and dependence. EDSS 10 indicates death which is MS-related.
to and including MS-related death. Scores on the EDSS appear to progress monotonically from perfect health (0) to MS-related death (10), which is a desirable measurement property. What the EDSS lacks, and never claimed to have, are cardinal measurement properties which permit arithmetic operations to be performed on it. One point changes in the EDSS, within different intervals on the EDSS, are not necessarily equivalent with respect to increase in disease burden. For example, an increase from 1 to 2 appears to be less burdensome than an increase from 6.5 to 7.5 on the EDSS. Despite its limitations the EDSS is useful in describing important elements of MS progression. Despite its limitations, the EDSS is the only standardized testing element that we have in both MS natural history studies and in the RCT study of Betaseron® treatment in MS, and is therefore the only outcome measure available to assess the efficacy of Betaseron® treatment on disability progression in MS within the context of MS natural history.

Although MS affects patients in many ways, all of which are important, only some of these disease features are measured by clinicians and by clinical studies. For instance, one major aspect of impairment and disability in these patients is loss of mobility. It is part of the clinical assessment, and a prominent element in the EDSS measurements in clinical trials. Other effects of the disease, such as altered self image, changed life plans, lost opportunities, altered relationships and marital strains, may be equally important, but are not usually measured in clinical trials. To some extent, the EDSS is a proxy for these other aspects, since one might infer that if the measured effects of the disease, such as impaired gait, weakness, sensory loss, need for walking aids, visual change, bladder control, and mental and emotional change were improved, the other psychosocial effects would also improve. Thus, when we assess the potential long term benefits of Betaseron®, we can assess only the measured elements that were improved, and can only speculate on whether the other important elements of the disease will similarly improve as a result.

Many studies have used EDSS measures to describe MS progression. In this study of Betaseron®, data from Runmarker and Anderson's 25 year prospective study of an MS incidence cohort of 308 persons are used to model MS progression. (Runmarker and Anderson, 1993) These Swedish data describe MS progression, using repeat EDSS measures and life-table methods. Their simplest analysis is stratified by gender, by MS classification at onset, and by the cumulative probability of reaching various EDSS endpoints (e.g., EDSS=6) from time of onset of MS symptoms to 25 years from time of onset. These MS natural history data are incorporated in the C/E model constructed to evaluate Betaseron®.

It is fortuitous that the EDSS=6.0 endpoint reported in the Runmarker and Anderson study
happens to coincide with Betaseron® RCT patient selection criteria, ie EDSS<6 for PwMS classified as relapsing remitting. In this study EDSS<6 scores are categorized as 'mild' disability and EDSS≥6 scores are categorized as 'severe' disability. Swedish natural history data are dichotomized using these definitions of 'mild' and 'severe' disabilities. Even this crude partitioning of stages of MS progression proves useful in analysing the health outcomes and economic consequences of therapies which retard the rate of MS disability progression.

A study of MS health care costs in Nova Scotia demonstrates that annual health care costs per PwMS increase as EDSS scores increase, and that mean annual health care costs per PwMS with EDSS<6 are substantially lower than those of per PwMS with EDSS≥6. Treatments which retard MS progression, therefore have economic consequences which partly offset direct treatment costs by delaying MS progression and associated higher health care costs. This is modelled in the C/E analyses presented below.

### 3.3 C/E Simulation Model of Betaseron® in MS

A cost / effectiveness simulation model of therapeutic and economic consequences of Betaseron® treatment in MS is developed using rate of progression of MS disability as the treatment outcome measure. The model builds upon a Swedish study of an MS incidence cohort of 308 persons followed prospectively for 25 years following onset. (Runmarker and Anderson) Among the many useful MS databases which have been used to analyse and describe MS natural history, this Swedish database is exceptional in being a comparatively large and representative MS incidence cohort, followed over an exceptionally long time, and where repeat MS-specific health status measures have been analysed using life-table methods. In the simulation model the Swedish data is projected to 40 years following onset in order to present a full life-cycle analysis. The model has nine components or modules:

1) MS Natural History Module
2) Health Policies Module (eligibility)
3) Treatment Management, Demand and Compliance Module
4) Treatment Efficacy Module (Betaseron®)
5) Health Outcomes Module
6) Direct Treatment Costs Module (Betaseron®)
7) Health Care Costs Foregone Module
8) Present Values Module
9) Cost / Effectiveness Module
This simulation model is a tool developed to facilitate economic evaluations of MS treatments and programs in general, and of Betaseron® in particular. The simulation model is implemented using spreadsheet software which facilitates asking and answering "what if..." questions and scenarios. This is done by selectively modifying parameter values which represent, for example,

<table>
<thead>
<tr>
<th>C/E Simulation Model Flow Chart</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) MS Natural History Module: Hypothetical MS Onset Cohorts of 1,000 Females and 1,000 Males; MS Disability Progression Modelled for 40 Years from Onset of Symptoms</td>
</tr>
<tr>
<td>+ 2) Health Policies Module (eligibility for treatment)</td>
</tr>
<tr>
<td>+ 3) Treatment Management, Demand and Compliance Module</td>
</tr>
<tr>
<td>= Number of Persons with MS Treated over MS Natural History, Years 1 - 40</td>
</tr>
<tr>
<td>+ 6) Direct Treatment Costs Module</td>
</tr>
<tr>
<td>+ 7) Health Care Costs Foregone Module, from a department of health perspective</td>
</tr>
<tr>
<td>= Estimates Net Treatment Program Costs ® in Years 1 - 40</td>
</tr>
<tr>
<td>+ 4) Treatment Efficacy Module (Betaseron®) in slowing MS disability progression</td>
</tr>
<tr>
<td>+ 5) Health Outcomes Module, Estimates E_{nEDSS-DYA} in Years 1 - 40</td>
</tr>
<tr>
<td>= Estimates Total Program Costs (C), Total Health Outcomes (E_{nEDSS-DYA}), C/E_{nEDSS-DYA} Ratios for Scenarios # 1 - #15, Undiscounted over Years 1 - 40</td>
</tr>
<tr>
<td>+ 8) Present Values Module, Discounting at 5%, with Sensitivity Analyses at 7.5% and 2.5%</td>
</tr>
<tr>
<td>= Estimated Present Values of Program Costs (C), Total Health Outcomes (E_{nEDSS-DYA}), and C/E_{nEDSS-DYA} Ratios for Scenarios # 1 - #15 from a Department of Health Perspective</td>
</tr>
</tbody>
</table>

treatment effect size, policy regarding eligibility for treatment, and patient compliance with treatment regimens over the long term. Each module within the simulation model performs particular functions, described below. The accounting relationships within the spreadsheet model are described in Appendix A. The flow chart of the C/E Simulation Model below shows where each module enters the model.
Appendix B contains tables which detail the C/E methods and results for Baseline Scenario #1. There are 20 spreadsheet tables for females and 20 for males. Summary tables which compare C/E results for basic Scenarios #1 - #6, and sensitivity analysis Scenarios #7 - #14, are presented both in this chapter and in Appendix B. Detailed tables for all 14 scenarios, comparable to the detailed tables for Scenario #1 found in Appendix B, are not presented since this would add little of substance.

Graphical methods are used to describe MS natural history paths, treatment effects, and C/E results whenever possible. Readers wishing further information about C/E methods used, and additional detail on intermediate results not reported in this chapter, should consult Appendices A and B.

The roles played by each module within the simulation model are described next.

3.3.1 MS Natural History Module

The MS natural history module uses data reported in Runmarker and Anderson, "Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up," to characterise MS progression. (Runmarker and Anderson, 1993) Data from Runmarker and Anderson’s Figures 1 and 3 (reproduced below) are supplemented by additional data (Table 1, kindly provided by Runmarker and Anderson) which describes MS progression, by gender, for PwMS classified at onset as having relapsing/remitting or progressive forms of MS. Trends in the Swedish MS progression data, from time of onset of MS symptoms to 25 years following onset, were projected to 40 years following onset. This was done to model the full natural history of MS from early age of onset to time of death related to MS.

The MS natural history module analyses separate hypothetical MS incidence cohorts for females (n=1000) and for males (n=1,000). Each cohort is stratified by mortality (Deaths/Survivors), MS classification (Relapsing Remitting / Chronic Progressive) and disability status (EDSS<6 “mild” disability / EDSS≥6 “severe” disability). The natural history module reflects MS progression in the Swedish MS incident cohort over 25 years, using life-tables methods, which describe:

1) the cumulative probability from onset of MS symptoms of reaching an endpoint of EDSS=10, representing MS-related death, for all persons with MS, (Runmarker & Anderson’s Figure 1)
2) the probability of being classified as Relapsing Remitting or Chronic Progressive at time of onset, by gender, (R&A, Figure 3, not reproduced here) and

3) the cumulative probability of becoming “severely” disabled (EDSS≥6) by years since onset, for PwMS classified as Relapsing Remitting or Chronic Progressive at time of onset, by gender.

Tables A and B (Appendix B) contain the above natural history data for females and males projected to 40 years from onset. These data are graphed in Figures 2 and 3 below, and are entered in Table A, Appendix B, “MS Natural History,” the first page of a cost/effectiveness spreadsheet model developed for this study.

The incidence and natural history of MS differs somewhat for females and males. Prevalence of MS is much greater among females (72% females, 28% males in Nova Scotia). MS classification at time of onset (and reclassification subsequent to onset) also differs by gender, with 91% of females and 79% of males being classified as relapsing remitting at time of onset. The cumulative probabilities or reaching given endpoints (e.g. EDSS=6) differs by gender and by MS classification, with slower progression for PwMS classified as relapsing remitting and faster progression for PwMS classified as progressive. In recognition of these and other important gender differences, and also for purposes of analytic convenience and generalizability, the natural history of MS in females and males is modelled separately in the natural history module.

Figures 2 and 3 shows the following MS natural history patterns.

First, cumulative mortality from time of onset of MS symptoms is low, reflecting both early disease onset (about 80% of MS incidence occurs by age 35) and low MS-related mortality which reduces life expectancy only slightly. For example, 25 years after onset 82% of the Swedish MS incidence cohort was alive. Projections to 40 years after onset show about 50% of females and 40% or males alive.
Table 1 Life Table Probabilities of Not Reaching End-point EDSS 6.0 in Patients with Definite or Probable MS, Classified at Onset of Symptoms

<table>
<thead>
<tr>
<th>Year</th>
<th>Definite &amp; Probable All Types of Onset</th>
<th>Definite &amp; Probable Bout Onset Only</th>
<th>Definite &amp; Probable PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
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<td>0.970</td>
<td>0.985</td>
</tr>
<tr>
<td>2</td>
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<td>0.977</td>
</tr>
<tr>
<td>3</td>
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<td>0.977</td>
</tr>
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</tr>
<tr>
<td>5</td>
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<td>0.799</td>
<td>0.947</td>
</tr>
<tr>
<td>6</td>
<td>0.901</td>
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<td>0.924</td>
</tr>
<tr>
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<td>0.645</td>
<td>0.917</td>
</tr>
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<td>0.615</td>
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<tr>
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<tr>
<td>25</td>
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<td>0.292</td>
<td>0.462</td>
</tr>
</tbody>
</table>

Note: Bout onset = relapsing remitting MS; PPMS (primary progressive MS) = chronic progressive MS. Source: B. Runmarker, Personal Communication, November 1995.
B. Runmarker and O. Andersen

Fig. 1. Prognosis in the whole incidence cohort, life table analysis with three different endpoints.

Fig. 2. Life-table analysis with endpoint DSS 6 in bout onset group and primary progressive group.
Figure 2: MS Natural History

Females

Years Since Onset

MS Onset Cohort

Deaths

MG Brown et al, Betaseron Study, CCOHTA, Dalhousie Univ.
Figure 3: MS Natural History

CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730  44
CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730  42
Second, at onset more females were classified as relapsing remitting (91%) than males (79%), with the balance classified as chronic progressive (females 9%, males 21%).

Third, the cumulative probability of progressing from “mild” MS-related disability (EDSS<6) to “severe” disability (EDSS≥6) is much lower for persons with MS who start and remain classified as relapsing remitting compared to those who start or are reclassified as chronic progressive. For example, 10 years after onset the cumulative probability of relapsing remitting PwMS reaching EDSS≥6 is \( Pr(EDSS≥6) = 0.22 \) while the cumulative probability of chronic progressives is \( Pr(EDSS≥6) = 0.79 \). (See columns for "Relapsing Remitting (bout onset), \( Pr(EDSS≥6) \)" and "Chronic Progressive (PPMS), \( Pr(EDSS≥6) \)" in Runmarker & Anderson's Table 1 above.)

In overview, Swedish MS natural history data - and other MS natural history studies - find that MS is characterized by early onset of symptoms; is predominantly a female disease; classification at onset of symptoms is typically 'relapsing remitting' rather than 'chronic progressive'; progression of MS disease activity typically results in reclassification from relapsing remitting to chronic progressive (not modelled in the present analysis); progression typically proceeds from mild to severe manifestations of MS-related disability and is much more rapid among persons classified as chronic progressive compared those classified as relapsing remitting. MS-related mortality is low and all-causes mortality is only moderately elevated in PwMS.

### 3.3.2 Health Policies Module

This module deals with public and private sector policies which affect access to health services in general and Betaseron® treatment in particular. These policies include Betaseron® treatment eligibility criteria. These might include clinical criteria such as definite diagnosis of MS, relapsing remitting; EDSS < 6, and criteria for termination of treatment eligibility. Changes in these criteria will increase or decrease the percent of persons with MS who are eligible to receive Betaseron® treatment paid for through public or private sector insurance plans. Public health policies regarding access to and the financing of other health services and social services, e.g., physicians services, hospital and diagnostic services, seniors pharmacare services, disability benefits and social security benefits, will indirectly impact on the C/E of Betaseron® treatment by modifying the size of public sector costs foregone given effective Betaseron® treatment.
3.3.3 Treatment Management, Demand and Compliance Module

This module deals with behavioural decisions by physicians and by PwMS regarding Betaseron® treatment. Physicians decisions regarding MS patient management options will determine the percent of PwMS eligible for Betaseron® treatment who are recommended to have treatment. Decisions by PwMS (and their families) will determine the percent of PwMS eligible for treatment who seek treatment (eg, demand Betaseron®) or, if treatment is recommended, accept treatment. Given that treatment calls for subcutaneous injections every other day for the rest of one life, or until treatment is discontinued for other reasons, such decisions are not likely to be made lightly.

i) MS Management decisions by physicians regarding Betaseron® treatment are modelled as the proportion of PwMS eligible for treatment who are recommended for treatment. A parameter value ranges from 0 - 1, where 0 indicates no eligible PwMS are recommended for treatment and 1 indicates all eligible PwMS are recommended for treatment. The perceived effectiveness of alternative treatments is believed to underlie MS management decisions, where effectiveness is conceived in holistic terms embracing the full spectrum of health and quality of life domains. MS management decisions are subject to periodic reassessment, at which time decisions may be taken to start, continue, or discontinue a particular treatment. In the case of new treatments such as Betaseron®, it is highly speculative to estimate the proportion of PwMS for whom a lifetime course of treatment will be recommended. It is also speculative at the present time to estimate the percent of PwMS who will choose to accept Betaseron® treatment if they are deemed eligible to receive it and if their physician recommends it. Projections of the percent of patients who will comply with the treatment regimen is also speculative. In addition, there is considerable uncertainty regarding the development of antibodies, following years of treatment, which may reduce treatment efficacy. Antibody development beyond a given threshold may lead physicians to recommend discontinuation of treatment. Similar criteria may also be incorporated in eligibility criteria for continuation of Betaseron® treatment.
ii) Demand for Betaseron treatment by PwMS may be a function of the types of health benefits and risks expected in years y=1,...,n and the relative values which they place on various type of health benefits. The values placed on risks perceived to be associated with treatment are equally important. The perceived treatment benefits and risks, together with the relative values of PwMS, will influence their decisions regarding whether or not to seek and continue treatment. Personal direct and indirect treatment costs and foregone costs are also expected to influence decisions. Patient time preferences regarding tradeoffs between present versus future costs and benefits will also influence decisions about whether to begin a life-long treatment program which has immediate psychic and economic costs, but whose future health benefits are not expected to be dramatic and are expected to delay progression, rather than to prevent progression, to more severe stages of the MS natural history.

iii) Compliance in the short and long run may also be a function of treatment user friendliness, side effects, toxicities, expected types of health benefits, patient relative values, patient time preferences and the burden of personal direct and indirect treatment costs. In the model reduced compliance, relative to compliance rates achieved under RCT conditions, is reflected as reductions in the percent of eligible persons who actually demand/utilize Betaseron. Ordinarily compliance falls over time. The Betaseron treatment regimen which requires subcutaneous injections every second day is not particularly user friendly.

In summary, the Treatment Management and Compliance Module models the percent of PwMS eligible for Betaseron treatment who are treated and who comply with the treatment regimen.

### 3.3.4 Treatment Efficacy Module (Betaseron)

This module incorporates evidence of Betaseron efficacy in slowing the rate of progression of MS disability, measured in the RCT using the EDSS. Betaseron treatment efficacy in slowing EDSS progression (E1) is entered as a 15% effect in baseline Scenario #1. This 15% effect should be interpreted as a treatment efficacy measure, rather than a treatment effectiveness measure, since it was achieved under favourable RCT conditions not likely to be experienced when Betaseron is used in a general MS population. Sensitivity analysis examines the consequences for C/E ratios of higher and lower efficacy effects.

If Betaseron slows the rate of MS disability progression by 15% then more time will be spent in each of the less severe disability states over the course of MS, and less time will be spent in at least the most severe disability state which would have been achieved in the absence of treatment. In the simplified C/E spreadsheet model, this treatment effect increases the number of years following MS onset to be spent in 'mild' disability categories (EDSS<6), and decreases the number of years spent in 'severe' disability categories (EDSS≥6). Graphically this treatment
effect is equivalent to an upward shift of an MS natural history curve plotted against HRQoL (Figure 1), or a rightward shift of the time path which plots the cumulative probability of reaching endpoint EDSS=6 in Figures 3 and 4, the MS natural history diagrams for cohorts of females and males based on Swedish data. Because the Betaseron® treatment effect on MS progression is measured using a normalized EDSS (nEDSS), the health outcome measure in the denominator (E) of the C/E analysis is **normalized EDSS-weighted Disability-Years-Avoided (E_{nEDSS-DYA}).**

The standard EDSS, (range 0 - 10) is divided by 10 to give a normalized, or rescaled range, nEDSS (range 0 - 1). The normalized EDSS (nEDSS) is used to weight a year of life (Y) by the severity of disability experienced in that year. In this study a disability-weighted year of life of a PwMS assessed as nEDSS="x" during that year is defined to be nEDSS-DY = "x", calculated by multiplying nEDSS by 1 year of life. For example, if a PwMS is assessment at nEDSS=0.4 throughout a year, for analytical purposes that year is weighted as 0.4 of a year with normal health. The disability-weighted years of a PwMS, or of an MS-onset cohort, may then be summed to describe total disability years experienced, or expected, over the natural history of MS. Disability-weighted years may also be used to describe the total number of disability-weighted-years-avoided (DYA) expected from treatments which slow the rate of disability progression in MS.

### 3.3.5 Health Outcomes Module (denominator of C/E ratio)

Health outcome effects for a hypothetical 1,000 person female MS incidence cohort and a 1,000 person male MS incident cohort are estimated in the C/E model using nEDSS-weighted disability years of life avoided (nEDSS-DYA) over 40 years following MS onset. This nEDSS-DYA outcome measure is analogous to an MS-specific Quality-Adjusted-Life-Year (QALY) gained outcome measure, but lacks the scaling and relative-value.properties expected in a well constructed QALY.

While Kurtzke's EDSS disability scale is subject to various technical criticisms regarding its measurement properties (eg Schwartz 1995a) the EDSS clearly distinguishes between relatively 'mild' (EDSS<6) and 'severe' (EDSS≥6) MS-related neurological and physical impairment. A practical reason for using EDSS measures in the C/E analysis is that they are used in MS clinics throughout the world, are widely used in characterizing MS natural history, and are collected as endpoints in RCTs.

In the C/E spreadsheet model total nEDSS-weighted disability years avoided due to effective treatment are estimated by subtracting total post-treatment nEDSS-disability years from total natural history nEDSS-disability years. Weights for EDSS<0.6 and EDSS≥0.6 are taken from
Nova Scotia MS clinic data, stratified by relapsing-remitting and chronic progressive classifications.

Given the nature of the categories incorporated in the EDSS, treatment outcomes measured in terms of EDSS-weighted disability years avoided will tend to be conservative estimates of perfectly-measured disability years avoided. There appears to be consensus that a one point increase on the EDSS scale, starting from a low EDSS score (eg 1.5), is in reality a less burdensome increase in MS-related disability (and a smaller decrease in health-related quality of life) than a one point increase on the EDSS scale starting from a higher EDSS score (eg 6.5). If this is indeed true, then the size of Betaseron® treatment health outcome effects, using EDSS-weighted MS-related disability years avoided, are biased downward.

The Swedish data which describe the cumulative probability of reaching particular disability endpoints, e.g., EDSS=6, are used (together with mean EDSS scores for EDSS<6 and for EDSS≥6 in Table 2) to calculate total normalized EDSS-weighted-disability-years experienced over the natural history of MS, from time of onset of MS symptoms to death. This is calculated separately for the hypothetical cohorts of 1,000 females and 1,000 males. Betaseron® RCT efficacy evidence is then used to estimates treatment effects measured in terms of normalized EDSS-weighted Disability-Years-Avoided (E_{nEDSS-DYA}) over the natural history of MS. The cumulative health benefits measured in this way correspond to the area between the natural history path (NH) and the treatment path (E1) in Figure 1.6

Despite EDSS deficiencies, E_{nEDSS-DYA} is the only health outcomes measure presently available for purposes of assessing Betaseron® treatment effects which slow disability progression. This is because the EDSS has been widely used in MS clinics and studies for many years, in contrast to more recent and sophisticated health status measures. EDSS data reported in MS natural history studies and in the Betaseron® RCT are combined with health care cost data to conduct a complete C/E analysis.

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6 In Figure 1, however, the Y-axis represents a generic health index which ranges from 0 - 1 (death to perfect health) whereas the normalized EDSS runs in the opposite direction, where 0 is perfect health and 1 is death related to MS. The normalized EDSS “disability” index can be expressed as a positive “disability-free” health index by subtracting the normalized EDSS from 1. The normalized EDSS can be graphed in Figure 1 to run in the same direction as a standard health index by defining the Y-axis as a “disability-free” health index = 1 - normalized EDSS), where a value of 1.0 represents perfect health (disability-free), a value of 0.05 represents extreme disability, and a value of 0 represents death related to MS.
Table 2. Mean EDSS scores by Relapsing-Remitting and Chronic Progressive MS, by Gender

<table>
<thead>
<tr>
<th></th>
<th>EDSS&lt;6</th>
<th></th>
<th>EDSS≥6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>females</td>
<td>males</td>
<td>females</td>
<td>males</td>
</tr>
<tr>
<td>Relapsing-Remitting</td>
<td>2.18</td>
<td>2.22</td>
<td>6.35</td>
<td>6.21</td>
</tr>
<tr>
<td>Chronic Progressive</td>
<td>3.81</td>
<td>3.68</td>
<td>6.88</td>
<td>6.83</td>
</tr>
</tbody>
</table>

Source: Dalhousie Multiple Sclerosis Integrated Database (MSID), clinical data (1980-1993). Used in C/E spreadsheet tables for Health Outcome Modules, Q in Appendix A.

Pre and post-Betaseron® treatment distributions of PwMS in “mild” and “severe” disability categories are graphed in Figures 4 - 9. The difference between "total natural history nEDSS-weighted years" experienced and "total post-treatment nEDSS-weighted years" experienced estimates "total nEDSS-weighted Disability-Years-Avoided" (E_{nEDSS-DYA}) due to Betaseron® treatment in the hypothetical 1000-person cohorts of females and of males during the 40 years from onset of MS symptoms.

The treatment effect estimates shown in Figures 4 - 9 are those estimated for baseline Scenario #1 (detailed below), derived by interacting: 1) the Natural History Module, 2) the Health Policies Module, 3) the Treatment Management, Demand and Compliance Module, and 4) the Treatment Efficacy Module, for females and males. (See Appendix B, see Tables A through F, for females and for males, for details of how these estimates were done.)

Estimated E_{nEDSS-DYA} is the health outcomes “effectiveness” measure (E) which enters as the denominator in C/E analyses. Health outcomes (E) are analysed in two ways, first, as simple totals over 40 years since onset, and second, as present value equivalents, using the same 5% real discount rate applied to net treatment costs.

3.3.6 Direct Treatment Costs Module (Betaseron®)

The direct treatment costs for Betaseron® used in the C/E analyses are based on unit prices approved in 1995 by the Canada Department of Health, Patented Medicines Price Review Board. Direct treatment costs, based on $91.427 per treatment every second day (365/2), total $16,685 CDN annually.
Figure 4: Treatment Effects

Relapsing Remitting & Chronic Progressive, Females

*Treatment Effect represents increase in 'mild' disability, or reduction in 'severe' disability, based on Scenario 1.

MG Brown et al, Betaseron Study, CCOHTA, Dalhousie Univ.
Figure 5: Treatment Effects

Relapsing Remitting & Chronic Progressive, Males

*Treatment Effect represents an increase in 'mild' disability, or a reduction in 'severe' disability, based on Scenario 1.

MG Brown et al, Betaseron Study, CCOHTA, Dalhousie Univ.
Figure 6: Treatment Effects
Relapsing Remitting, Females

* Treatment Effect represents an increase in 'mild' disability, or reduction in 'severe' disability.

MG Brown et al. Betaseron Study, COHTA, Dalhousie Univ.
Figure 7: Treatment Effects

Relapsing Remitting, Males

* Treatment Effect represents an increase in 'mild' disability, or reduction in 'severe' disability.

MG Brown et al, Betaseron Study, CCOHTA, Dalhousie Univ
Figure 8: Treatment Effects

Chronic Progressive, Females

* Treatment Effect represents increase in 'mild' disability, or reduction in 'severe' disability.

MG Brown et al, Betaseron Study, CCOHTA, Dalhousie Univ.
Figure 9: Treatment Effects

Chronic Progressive, Males

Deaths

EDSS-6, 'Severe' Disability

Treatmen Effect

EDSS-6, Mild Disability

Years Since Onset

MS Onset Cohort

* Treatment Effect represents increase in 'mild' disability, or reduction in 'severe' disability.
This assumes each PwMS gets the same dose, which likely will not occur. Actual prices may also differ, if bulk purchases are negotiated by payers, or if competition from competing drugs emerges. In the model it is assumed that treatment, and treatment cost, ceases when a person receiving treatment ceases to comply with the treatment regimen.

In baseline Scenario # 1 Betaseron® treatment is modelled to begin following a “definite diagnosis of MS”, in the third year following onset of MS symptoms. Treatment is modelled to continue until a PwMS is assessed as EDSS≥6 in two consecutive years, unless explicitly modelled otherwise, e.g., where eligibility for treatment is discontinued following a buildup of antibodies beyond a given threshold. The criteria for starting treatment (i.e. a definite diagnosis of MS) and for discontinuing treatment (i.e. after a PwMS is no longer ambulatory without aids), reflect recommendations of a panel of Canadian neurologists published in December 1995. (Oger J, 1995) These recommended appear to be based on the selection criteria used in the Betaseron® RCT.

3.3.7 Health Care Costs Foregone Module

Public sector health care costs foregone per year by PwMS who benefit from Betaseron® treatment are calculated using Nova Scotia “Medicare” data, and is presented in two ways. Annual health care costs per utilizer are calculated using as the denominator only those PwMS who utilized particular health services (MD, HOSP, PHARM) during the year. Annual health care costs per PwMS at risk are calculated using as the denominator all PwMS at risk during a year, based on estimates of MS prevalence in Nova Scotia for period 1989/90-1993/94. MS prevalence in Nova Scotia was estimated from MS diagnostic codes included in hospital separation and physicians services administrative databases. (Brown et al, 1996)

When almost all persons in a population at risk use particular health services during a year (eg MD services and seniors' pharmacare benefits) the difference between PwMS costs per utilizer and costs per PwMS at risk is quite small. However, in the case of hospital inpatient and day surgery, PwMS costs per utilizer are almost four times higher than costs per PwMS at risk. This is because only 27% or PwMS have one or more hospital separations per year. This 27% hospital separation rate for PwMS, however, is 69% higher than the 16% hospital separation rate for the Nova Scotia population at large.

Estimates of “costs foregone” due to Betaseron® treatment effects which slow rate of disability progression are based on observed differences in health care costs between PwMS having “mild” versus "severe" disabilities. Annual total public sector health care costs are computed using Nova
Scotia public sector 'Medicare' programs which are universal and comprehensive coverage programs which encompass physicians' services, hospital and diagnostic services, and seniors pharmacare benefits. By linking MS clinic visits data, which include EDSS scores, to "Medicare" data it is possible to document difference in health care resource utilization by PwMS as a function of disability severity. Detailed MS cost data of this type are reported in "MS Health Care Costs in Nova Scotia: A Population-Based Life-Cycle Study." (Brown et al, 1996 forthcoming) This study developed a Multiple Sclerosis Integrated Database (MSID), which links MS clinic data (1980-1993) and Medicare data (1989/90 - 1993/94). This MSID enabled calculation of public sector Medicare costs per year per PwMS, stratified by gender (f/m), MS classification (rr/cp), MS-related neurological and physical disability (EDSS<6/EDSS≥6), and other clinical and PwMS variables. Table 3 shows public sector health care costs per year per PwMS, stratified by “mild” and “severe” disability.

### Table 3: Public Sector Health Care Costs per Person with MS per Year:
**Physicians Services, Hospital & Diagnostic Services, Seniors Pharmacare Benefits in Nova Scotia, 1989-90 - 1993/94**
Utilizer & Population-at-Risk Basis, by EDSS and Gender

<table>
<thead>
<tr>
<th></th>
<th>Physicians Services</th>
<th>Hospital Services Utilizers</th>
<th>Hospital Services Population-at-Risk</th>
<th>Seniors Pharmacare Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient</td>
<td>Outpatient</td>
<td>Inpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS&lt;6.0</td>
<td>$561.42</td>
<td>$4,628.05</td>
<td>$689.02</td>
<td>$618.08</td>
</tr>
<tr>
<td>EDSS≥6.0</td>
<td>$684.42</td>
<td>$9,309.52</td>
<td>$809.52</td>
<td>$1,942.05</td>
</tr>
<tr>
<td>EDSS=10</td>
<td>$1,333.54</td>
<td>$38,250.00</td>
<td>$83.33</td>
<td>$15,300.00</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS&lt;6.0</td>
<td>$512.11</td>
<td>$2,833.33</td>
<td>$666.67</td>
<td>$281.46</td>
</tr>
<tr>
<td>EDSS≥6.0</td>
<td>$846.51</td>
<td>$15,233.33</td>
<td>$1,433.33</td>
<td>$2,967.53</td>
</tr>
<tr>
<td>EDSS=10</td>
<td>$566.87</td>
<td>$500.00</td>
<td>$2,000.00</td>
<td>$50.00</td>
</tr>
</tbody>
</table>

Source: NS MSID, 1989-93
For resource management decisions at the level of the individual patient, cost per utilizer is ordinarily the appropriate perspective. For resource management decisions at the program level, cost per person at risk is ordinarily the appropriate perspective.

3.3.8 Present Values Module

Present values at time of MS onset are calculated for both net treatment costs (numerator) and net health benefits (denominator) using standard discount formulae. A 5% real discount rate is used in baseline Scenario # 1. Discount rates of 2.5% and 7.5% are used in other scenarios as part of a sensitivity analysis of C/E results.

3.3.9 Cost/Effectiveness (C/E) Module

The cost/effectiveness (C/E) module encapsulates data and methods included in all other modules. The numerator C summarizes MS net treatment program costs. The denominator E summarizes health outcomes. The ratio C/E summarized in a single number the expected net costs per unit of health outcome improvement achieved. For purposes of analysing Betaseron® treatment costs on MS disability progression the C/E ratio may be expressed as:

\[
C/E = (\text{Direct Treatment Costs} - \text{Foregone Costs}) / n\text{EDSS Disability-Years-Avoided}
\]

Net costs are expressed in either current dollars, or as present values at time of MS onset after discounting both cost and health benefit streams using 5%, 7.5% and 2.5% discount rates.

Health outcomes in C/E analyses may be expressed in natural units for a single health outcome dimension (e.g. disability years avoided) or as an index number (health index), which is a weighted average of health outcomes encompassing more than one health dimension.

Health outcomes may be expressed as simple summations of health outcome streams following treatment (i.e. equivalent to summing current dollar costs), or expressed as present value equivalents of health outcome streams. For purposes of program evaluation the more relevant expression of both program costs and health outcomes is in terms of present values.

Treatment effects, which slow disability progression, thereby keeping PwMS at mild disability levels (EDSS<6) for longer periods, generate foregone health care costs. Nova Scotia data demonstrate that annual health care costs of those in 'severe' MS-related disability categories are much greater than those in 'mild' MS-related disability categories. (Table 3) Slower disability
progression means reduced life-time health care costs per PwMS, in terms of both current dollars and dollars discounted to time of onset.

3.4 Empirical Foundations of C/E Analysis of Betaseron®

The C/E analysis of Betaseron® in MS is founded on the following empirical data:

- The *MS natural history module* is based on life-tables analyses of a Swedish MS onset cohort of 308 PwMS followed prospectively for 25 years, with MS progression measured by EDSS. (Runmarker and Anderson, 1993) For purposes of C/E analyses, the Swedish data were projected for another 15 years.

- *Betaseron® RCT efficacy evidence* over 5 years, including EDSS progression. (IBNF, 1993, IBNF, 1995)

- *Betaseron® Treatment Cost per PwMS per year* ($16,865) is based on a maximum price approved by the Canada Department of Health, Patented Medicines Price Review Board in 1995.

- *Foregone public sector direct health care costs per PwMS per year* are estimated from Nova Scotia Department of Health administrative databases for major 'Medicare' programs, which are tax financed, universal coverage, comprehensive, zero copay (excepting Seniors Pharmacare benefits) health care programs. These cost data are stratified by PwMS in 'mild' and 'severe' EDSS categories and by gender. The difference between public sector health care costs by PwMS in 'severe' versus 'mild' disability categories is used to estimate total foregone direct health care costs which may be foregone due to Betaseron® treatment effects which slows disability progression. Generation of such health care cost data for PwMS, stratified by stage of MS disability progression, was made possible through creation of the Nova Scotia 'Multiple Sclerosis Integrated Database' (MSID), which links DMSRU clinical data (1980-1993) to Nova Scotia 'Medicare' data (1989/90 - 1993/94), using scrambled personal identifiers. Table 3 summarizes the structure and content of the Nova Scotia MSID. A complete description of this database is contained in a forthcoming report of Multiple Sclerosis Health Care Costs in Nova Scotia. (Brown et al, 1996)
### Table 4. Multiple Sclerosis Integrated Database (MSID) Flow Chart

<table>
<thead>
<tr>
<th>Dalhousie Multiple Sclerosis Research (DMSRU)</th>
<th>Nova Scotia Dept. of Health Utilization Data (All ID's scrambled)</th>
<th>MSI Seniors’ Pharmacare Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=548*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisk et al Study DMSRU subset:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989-1991, N=193</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Table 4 notes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) * Shows DMSRU study group population at risk in a given year. Maximum linkage of MS health cost study cases is N=548, for all ages, and is N=65 for seniors, age 65 or more. Mortality and migration account for most non-linkages.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Bold numbers in File A indicate linkages achieved between DMSRU study group persons with MS and their DOH health services utilization records. (3) Bold numbers in File B show linkages of &quot;other&quot; persons with MS to DOH utilization data. (4) Bold numbers in File C show total number of utilizers of DOH &quot;Medicare&quot; programs by all Nova Scotians.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) fn:msreport/chart1; Source: Dalhousie MS Cost Study. fn:msreport/chart1 95.10.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Multiple Sclerosis Integrated Database (MSID)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FILE A: DMSRU MS Case Observations / year</strong></td>
</tr>
<tr>
<td>1990/91 N=469 *</td>
</tr>
<tr>
<td>N=1993 &quot;Other&quot; PwMS in File B</td>
</tr>
<tr>
<td>1989/90 N=1,659</td>
</tr>
<tr>
<td>1990/91 N=1,678</td>
</tr>
<tr>
<td>1992/93 N=1,679</td>
</tr>
<tr>
<td>1993/94 N=1,656</td>
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<tr>
<td>1989/90 N=1,659</td>
</tr>
<tr>
<td>1990/91 N=1,678</td>
</tr>
<tr>
<td>1991/92 N=1,701</td>
</tr>
<tr>
<td><strong>FILE B: &quot;OTHER&quot; MS Case Observations / Year</strong></td>
</tr>
<tr>
<td>N=918,100 persons in Nova Scotia, Census July 1, 1991</td>
</tr>
<tr>
<td>1989/90 N=800,713</td>
</tr>
<tr>
<td>1990/90 N=807,967</td>
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<tr>
<td>1993/94 N=815,149</td>
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<tr>
<td>1990/91 N=107,808</td>
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<tr>
<td>1992/93 N=107,808</td>
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</table>

Table 3 notes: (1) * Shows DMSRU study group population at risk in a given year. Maximum linkage of MS health cost study cases is N=548, for all ages, and is N=65 for seniors, age 65 or more. Mortality and migration account for most non-linkages. (2) Bold numbers in File A indicate linkages achieved between DMSRU study group persons with MS and their DOH health services utilization records. (3) Bold numbers in File B show linkages of "other" persons with MS to DOH utilization data. (4) Bold numbers in File C show total number of utilizers of DOH "Medicare" programs by all Nova Scotians. fn:msreport/chart1; Source: Dalhousie MS Cost Study. fn:msreport/chart1 95.10.06
3.5 Betaseron® C/E Analysis Results

3.5.1 Program Costs and Cost per (normalized) EDSS-Disability-Year-Avoided (nEDSS-DYA)

Table 4 both describes Scenarios #1 to #15 and summarizes C/E results for these scenarios. Table 4.1 describes 15 scenarios analysed, which differ from one another in various ways and which include "sensitivity analysis" scenarios. Table 4.2 compares scenario results for a hypothetical MS onset cohort of 1,000 females. Table 4.3 compares scenario results for a hypothetical cohort of 1,000 males. MS natural history progression, as measured by normalized EDSS scores, are taken from Runmarker and Anderson's study of an MS onset cohort followed for 25 years. (Runmarker & Andersen, 1993)

Results are reported two ways, first, on a health care cost/utilizer basis, and second, on a health care cost per PwMS at risk basis. Because annual costs per (hospital) utilizer are much greater than annual costs per PwMS at risk, health care costs foregone following effective treatment are greater for utilizers, net treatment costs are lower, and C/E ratios are lower.

Results for females and males differ somewhat, reflecting gender differences in MS natural history. Blended C/E results for a hypothetical MS onset cohort of 1,000 persons with MS (females and males) may be calculated using a weighted average of C/E results for females (with a weight of .72) and C/E results for males (with a weight of .28). These weights reflect the gender distribution at time of MS onset within Nova Scotia's DMSRU database. Jurisdictions with a different gender distribution may apply their own weights.

The following description of Scenarios 1 - 15 is designed to help the reader interpret the Scenario descriptions summarized in Table 2, 'pages 1 - 3'. Scenarios # 1 - #13 model the treatment of PwMS classified as relapsing-remitting (rr) at onset. Scenario #1 serves as a 'baseline scenario.' Scenario #2 - #13 are variations of Scenario #1 and include certain sensitivity analyses. Scenario # 14 models the treatment of PwMS classified as progressive (cp) at onset, using scenario parameters identical to Scenario #1. Scenario # 15 combines Scenario #1 and #14 by modelling the treatment of PwMS classified as either rr or cp at onset, using scenario parameters identical to Scenario #1.

Scenario #1 sets eligibility for treatment to include only PwMS classified as rr. It sets treatment efficacy with respect to reduced EDSS progression (T1) at the upper bound of 5 year RCT results. Setting the treatment effect at T1= .85 reduces the rate of EDSS progression to .85 of the natural history rate of EDSS progression, which increases the time elapsed to progress from a
“mild” to a “severe” disability category by about 15%. All other treatment eligibility, MS management, demand and compliance parameters are given maximum values so that all persons with MS are eligible for Betaseron® treatment, demand treatment and comply with treatment regimens. Scenario #1 is referred to as the “baseline scenario’. Eligibility for treatment is contingent upon a definite diagnosis of MS, which is modelled to occur within two years of onset of MS symptoms, with treatment modelled to start in the third year following onset. Eligibility for treatment is modelled to cease two years after a PwMS becomes "severely" disabled, being assessed as EDSS≥6 in two consecutive years.

Scenario #2 (rr only) sets T1=.85; compliance after 5 years is C=.45, that achieved under RCT conditions; once a person becomes non-compliant they cease to receive treatment.

Scenario #3 (rr only) sets T1=.85; compliance after 5 years is C=.20, which may be a realistic estimate under ordinary conditions.

Scenario #4 (rr only) sets T1=.85 for treatment years 1-5, after which the buildup of antibodies in about 40% of PwMS treated renders further treatment ineffective; in this scenario eligibility for treatment criteria include all PwMS for years 1-5, but eligibility could be modelled to be contingent upon antibody status; physician MS management which take into account antibodies is modelled to reduced the number of PwMS after five years to 60% of those who started treatment; compliance is C=1.0 for those treated.

Scenario #5 (rr only) sets T1=.85; eligibility is relapsing-remitting only, with EDSS<6; a user copayment rate 20% is set, which is modelled to reduce demand by 20% assuming a price elasticity of demand equal to one.

Sensitivity Analyses:
Scenarios #6 - #13 provide a type of sensitivity analysis of Scenarios #1 - #5.

Scenario #6 (rr only) sets the treatment effect on EDSS progression at 7.5%, half that used in baseline Scenario #1.

Scenario #7 (rr only) sets the treatment effect on EDSS progression at 22.5%, double that used in baseline Scenario #1.

Scenario #8 (rr only) is equivalent to Scenario #1, but with the discount rate set to 2.5%.
Scenario #9 (rr only) is equivalent to Scenario #1, but with the discount rate set to 7.5%.
Scenario #10 (rr only) is equivalent to Scenario #1, but with health care costs doubled (200%).

Scenario #11 (rr only) is equivalent to Scenario #1, but with health care costs reduced to 50% of their former level.

Scenario #12 (rr only) is equivalent to Scenario #1, but with direct treatment costs reduced to $12,201 PwMS treated per year, or 75% of their former level.

Scenario #13 (rr only) is equivalent to Scenario #1, but treatment continues indefinitely rather than being discontinued 2 years after EDSS\geq6 is reached.

Scenario #14 (cp only) is identical to Scenario #1, but models only the treatment of PwMS classified as progressive from onset of symptoms.

Scenario #15 (rr + cp) is also identical to Scenario #1, but models the treatment of both PwMS classified as rr at onset and those classified as cp at onset.
### Table 5.1-1 DESCRIPTIONS OF SCENARIOS #1 TO # 5

<table>
<thead>
<tr>
<th>MS Onset Cohorts, EDSS Progression Modelled Over 40 Years</th>
<th>Parameter range, units</th>
<th>Scenario Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td># 1</td>
</tr>
</tbody>
</table>

#### A. TREATMENT EFFECTS

1.1 Treatment Effect T1

\[
T1 = E1 \times \text{PrEDSS} \geq 6
\]

where E1 is treatment efficacy, measured by reduced probability of reaching endpoint EDSS ≥ 6; model for rr and/or cp

- range: 0 - 1
- E1 = 0, 100% efficacy (prevention)
- E1 = 1, 0% efficacy
- Note: E1 = 1 when EDSS ≥ 6

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1=.85 RCT upper bound</td>
<td>T1=.85</td>
<td>T1=.85</td>
<td>T1=.85</td>
<td>T1=.85</td>
<td></td>
</tr>
</tbody>
</table>

#### B. PERSONS WITH MS TREATED, Nt = Ncohort x EL x M x D x C, where Nt = # treated, Y = 0-40

2.1 Treatment Eligibility Policies (EL), Public/Private Insurance: rr and/or cp, when MS diagnosed (2 years after onset), discontinued 2 years after EDSS = 6.0

- range: 0 - 1
- 0 = 0% eligible
- 1 = 100% eligible

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>EL=1, rr only</td>
<td>EL=1, rr only</td>
<td>EL=1, rr only</td>
<td>EL=1, rr only</td>
<td>EL=1, rr only</td>
<td></td>
</tr>
</tbody>
</table>

2.2 MS Management (M)

- % PwMS treated by MD

- range: 0 - 1
- 0 = 0% treated
- 1 = 100% treat

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>M=1</td>
<td>M=1</td>
<td>M=1</td>
<td>M=1, Y=2-6</td>
<td>M=.6, Y&gt;6</td>
<td></td>
</tr>
</tbody>
</table>

2.3 Treatment demand (D) by PwMS

- range: 0 - 1
- 0 = nil; 1 = 100%

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>D=1</td>
<td>D=1</td>
<td>D=1</td>
<td>D=1</td>
<td>D=.8, CoPay=.2</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Compliance by PwMS Treated

- range: 0 - 1
- 0 = nil; 1 = 100%

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>C=1</td>
<td>C=.45</td>
<td>C=.2</td>
<td>C=1</td>
<td>C=.45</td>
<td></td>
</tr>
</tbody>
</table>

#### C. SENSITIVITY ANALYSIS

2.5 Annual Direct Costs per PwMS Treated

percentage of baseline

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

2.6 Discount Rate

0% - 100%

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

2.7 Health Care Costs

percentage of baseline

<table>
<thead>
<tr>
<th></th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.1-2 DESCRIPTIONS OF SCENARIOS #6 TO #10

<table>
<thead>
<tr>
<th>MS Onset Cohorts, EDSS Progression Modelled Over 40 Years</th>
<th>Parameter range, units</th>
<th>Scenario Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td># 6</td>
<td># 7</td>
<td># 8</td>
</tr>
</tbody>
</table>

#### A. TREATMENT EFFECTS

1.1 Treatment Effect T1

- **T1=E1rrPrEDSS≥6**
- **T1=E1cpPrEDSS≥6,** where E1 is treatment efficacy, measured by reduced probability of reaching endpoint EDSS≥6; model for rr and/or cp

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1=.925</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1=.775</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1=.85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### B. PERSONS WITH MS TREATED, Nt=Neohort x EL x M x D x C, where Nt= # treated, Y=0-40

2.1 Treatment Eligibility Policies (EL), Public/Private Insurance: rr and/or cp, when MS diagnosed (2 years after onset), discontinued 2 years after EDSS=6.0

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>EL=1, rr only</td>
<td></td>
<td></td>
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<tr>
<td>EL=1, rr only</td>
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<td></td>
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</tbody>
</table>

2.2 MS Management (M)

% PwMS treated by MD

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>M=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3 Treatment demand (D) by PwMS

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>D=1</td>
<td></td>
<td></td>
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</tr>
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</table>

2.4 Compliance by PwMS Treated

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>C=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

#### C. SENSITIVITY ANALYSIS

2.5 Annual Direct Costs per PwMS Treated

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.6 Discount Rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% - 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.7 Health Care Costs

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730  64
Table 5.1-3 DESCRIPTIONS OF SCENARIOS #11 TO #15

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scenario Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range, units</td>
<td># 11</td>
</tr>
</tbody>
</table>

### A. TREATMENT EFFECTS

1.1 Treatment Effect $T_1$

- $T_1 = E_{1rrPrEDSS \geq 6}$
- $T_1 = E_{1cpPrEDSS \geq 6}$, where $E_1$ is treatment efficacy, measured by reduced probability of reaching endpoint $EDSS \geq 6$; model for $rr$ and/or $cp$

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>.85</td>
<td>.85</td>
<td>.85</td>
<td>.85</td>
<td>.85</td>
</tr>
</tbody>
</table>

### B. PERSONS WITH MS TREATED, $N_t = N_{cohort} \times E_{L} \times M \times D \times C$, where $N_t = \#$ treated, $Y = 0-40$

2.1 Treatment Eligibility Policies ($E_{L}$), Public/Private Insurance: $rr$ and/or $cp$, when MS diagnosed (2 years after onset), discontinued 2 years after $EDSS = 6.0$

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{L}$</td>
<td>$0%$</td>
<td>$0%$</td>
<td>$100%$</td>
<td>$0%$</td>
<td>$100%$</td>
</tr>
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</table>

2.2 MS Management ($M$) % PwMS treated by MD

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
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</tbody>
</table>

2.3 Treatment demand ($D$) by PwMS

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
</tr>
</tbody>
</table>

2.4 Compliance by PwMS Treated

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
</tr>
</tbody>
</table>

### C. SENSITIVITY ANALYSIS

2.5 Annual Direct Costs per PwMS Treated percentage of baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$100%$</td>
<td>$75%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
</tr>
</tbody>
</table>

2.6 Discount Rate 0% - 100%

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0%$</td>
<td>$5%$</td>
<td>$5%$</td>
<td>$5%$</td>
<td>$5%$</td>
<td>$5%$</td>
</tr>
</tbody>
</table>

2.7 Health Care Costs percentage of baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
<td>$100%$</td>
</tr>
<tr>
<td>MS Onset Cohort, EDSS Progression Modelled Over 40 Years</td>
<td>Units</td>
<td>Scenarios</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>-------</td>
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<td></td>
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<td></td>
<td></td>
<td># 1</td>
<td># 2</td>
<td># 3</td>
<td># 4</td>
</tr>
<tr>
<td>Table 5.2-1 COST/EFFECTIVENESS SCENARIO RESULTS FOR FEMALES (Scenarios #1 to #5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### (a) PROGRAM COSTS (C) (Current Canadian dollars)

<table>
<thead>
<tr>
<th># PwMS Treated</th>
<th># PwMS</th>
<th>910</th>
<th>410</th>
<th>Y2</th>
<th>910</th>
<th>Y2</th>
<th>910</th>
</tr>
</thead>
<tbody>
<tr>
<td>$</td>
<td>$</td>
<td>355,032,526</td>
<td>159,829,710</td>
<td>70,829,640</td>
<td>243,006,566</td>
<td>127,777,004</td>
<td></td>
</tr>
<tr>
<td>Treatment Costs</td>
<td>$</td>
<td>8,999,679</td>
<td>3,986,060</td>
<td>1,764,898</td>
<td>5,399,526</td>
<td>3,207,914</td>
<td></td>
</tr>
<tr>
<td>HC Cost Foregone</td>
<td>$</td>
<td>2,781,249</td>
<td>1,230,000</td>
<td>542,757</td>
<td>1,667,336</td>
<td>989,236</td>
<td></td>
</tr>
<tr>
<td>Net Costs</td>
<td>$</td>
<td>346,032,847</td>
<td>155,843,650</td>
<td>69,064,742</td>
<td>237,607,040</td>
<td>124,569,089</td>
<td></td>
</tr>
</tbody>
</table>

### HEALTH OUTCOMES (E) : EDSS-DYA = Normalized EDSS-Disability-Years-Avoided = E_{EDSS-QALY}

| Total EDSS-DYA | # EDSS-DYA | 761 | 336 | 148 | 456 | 270 |
| Expected EDSS-DYA | # EDSS-DYA | 0.84 | 0.82 | 0.21 | 0.50 |

### COST/EFFECTIVENESS RATIOS : C/EDSS-QALY (Current dollars)

<table>
<thead>
<tr>
<th>Cost/EDSS-DYA</th>
<th>Cost / EDSS-DYA</th>
<th>454,897</th>
<th>463,575</th>
<th>466,304</th>
<th>521,232</th>
<th>460,869</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) per utilizer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td></td>
<td>463,072</td>
<td>471,773</td>
<td>474,555</td>
<td>529,419</td>
<td>469,077</td>
</tr>
</tbody>
</table>

### (b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET

<table>
<thead>
<tr>
<th>Treatment Costs</th>
<th>$</th>
<th>180,711,669</th>
<th>81,441,948</th>
<th>36,121,196</th>
<th>133,203,567</th>
<th>65,119,853</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC Cost Foregone</td>
<td>$</td>
<td>2,891,890</td>
<td>1,287,982</td>
<td>588,285</td>
<td>1,771,768</td>
<td>1,048,638</td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>892,137</td>
<td>395,877</td>
<td>179,386</td>
<td>545,564</td>
<td>321,822</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>177,819,779</td>
<td>80,153,966</td>
<td>35,532,911</td>
<td>131,431,799</td>
<td>64,071,215</td>
</tr>
</tbody>
</table>

### HEALTH OUTCOMES, PRESENT VALUES

| Total EDSS-DYA | EDSS-DYA | 244 | 108 | 49 | 149 | 88 |
| Expected EDSS-DYA | EDSS-DYA | 0.27 | 0.26 | Y2  | 0.07 Y≤6 0.16 |
| a) per utilizer |                |       |     | Y>5 | 0.27 Y>6 | 0.27 |
| b) per PwMS at Risk |            | 729,007 | 741,364 | 727,045 | 881,624 | 729,313 |

### COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)

<table>
<thead>
<tr>
<th>Cost/EDSS-DYA</th>
<th>$/ EDSS-DYA</th>
<th>737,205</th>
<th>749,616</th>
<th>735,411</th>
<th>889,849</th>
<th>737,586</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) per utilizer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td></td>
<td>729,007</td>
<td>741,364</td>
<td>727,045</td>
<td>881,624</td>
<td>729,313</td>
</tr>
</tbody>
</table>

---

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### Table 5.2-2 COST/EFFECTIVENESS SCENARIO RESULTS FOR FEMALES (Scenarios #6 to # 10)

<table>
<thead>
<tr>
<th>MS Onset Cohort, EDSS Progression Modelled Over 40 Years</th>
<th>Scenarios Units</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) PROGRAM COSTS (C) (Current Canadian dollars)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 PwMS Treated</td>
<td>$</td>
<td>910</td>
<td>910</td>
<td>910</td>
<td>910</td>
<td>910</td>
</tr>
<tr>
<td>3.2 Treatment Costs</td>
<td>$</td>
<td>341,000,082</td>
<td>369,131,713</td>
<td>355,032,526</td>
<td>355,032,526</td>
<td>355,032,526</td>
</tr>
<tr>
<td>3.3 HC Cost Foregone</td>
<td>$</td>
<td>4,552,431</td>
<td>13,471,552</td>
<td>8,999,679</td>
<td>8,999,679</td>
<td>17,999,358</td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>1,405,239</td>
<td>4,164,877</td>
<td>2,781,249</td>
<td>2,781,249</td>
<td>5,557,152</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>336,447,651</td>
<td>355,660,161</td>
<td>346,032,847</td>
<td>346,032,847</td>
<td>337,033,168</td>
</tr>
<tr>
<td>3.4 Net Costs</td>
<td>$</td>
<td>339,594,843</td>
<td>364,966,836</td>
<td>352,251,278</td>
<td>352,251,278</td>
<td>349,475,374</td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>336,447,651</td>
<td>355,660,161</td>
<td>346,032,847</td>
<td>346,032,847</td>
<td>337,033,168</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>339,594,843</td>
<td>364,966,836</td>
<td>352,251,278</td>
<td>352,251,278</td>
<td>349,475,374</td>
</tr>
</tbody>
</table>

#### HEALTH OUTCOMES (E): EDSS-DYA = Normalized EDSS-Disability-Years-Avoided = $E_{\text{EDSS-QALY}}$

| 3.5 Total EDSS-DYA                                      | # EDSS-DYA      | 384 | 1,139 | 761 | 761 | 761 |
| 3.6 Expected EDSS-DYA per PwMS Treated                 | # EDSS-DYA      | 0.42 | 1.25  | 0.84 | 0.84 | 0.84 |

#### COST/EFFECTIVENESS RATIOS: $C/E_{\text{EDSS-QALY}}$ (current dollars)

| 3.7 Cost/EDSS-DYA                                       | Cost / EDSS-DYA | 875862 | 312,169 | 454,897 | 454,897 | 443,066 |
| a) per utilizer                                         |                 | 884055 | 320,337 | 463,072 | 463,072 | 459,423 |
| b) per PwMS at Risk                                    |                 | 875862 | 312,169 | 454,897 | 454,897 | 443,066 |

#### (b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET

| 3.1 Treatment Costs                                     | $               | 176506771 | 184,919,391 | 245,633,750 | 139,517,495 | 180,711,669 |
| 3.2 HC Cost Foregone                                    | $               | 1479072 | 4,306,361 | 4,930,616 | 1,807,052 | 5,783,779 |
| a) per utilizer                                         | $               | 455002 | 1,329,785 | 1,522,618 | 556,753 | 1,781,488 |
| b) per PwMS at Risk                                    | $               | 175027699 | 180,613,030 | 240,703,134 | 137,710,443 | 174,927,889 |

#### HEALTH OUTCOMES, PRESENT VALUES

| 3.4 Total EDSS-DYA                                      | EDSS-DYA        | 124 | 364  | 416  | 152  | 244  |
| 3.5 Expected EDSS-DYA per PwMS Treated                 | EDSS-DYA        | 0.14 | 0.40  | 0.46  | 0.17  | 0.27  |

#### COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)

| 3.6 Cost/EDSS-DYA                                       | $/EDSS-DYA      | 1408146 | 496,620 | 578,107 | 904,703 | 717,151 |
| a) per utilizer                                         | $/EDSS-DYA      | 1416385 | 504,804 | 586,292 | 912,917 | 733,559 |
### Table 5.2-3 COST/EFFECTIVENESS SCENARIO RESULTS FOR FEMALES (Scenarios # 11 to # 15)

<table>
<thead>
<tr>
<th>MS Onset Cohort, EDSS Progression Modelled Over 40 Years</th>
<th>Units</th>
<th>Scenarios</th>
<th># 11</th>
<th># 12</th>
<th># 13</th>
<th># 14</th>
<th># 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) PROGRAM COSTS (C) (Current Canadian dollars)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 PwMS Treated</td>
<td>$</td>
<td>910</td>
<td>910</td>
<td>910</td>
<td>90</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>3.2 Treatment Costs</td>
<td>$</td>
<td>355,032,526</td>
<td>266,274,395</td>
<td>502,882,099</td>
<td>15,700,987</td>
<td>370,733,514</td>
<td></td>
</tr>
<tr>
<td>3.3 HC Cost Foregone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>4,499,840</td>
<td>8,999,679</td>
<td>8,859,234</td>
<td>1,316,726</td>
<td>10,250,622</td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>1,393,297</td>
<td>2,781,249</td>
<td>2,744,909</td>
<td>404,089</td>
<td>3,168,299</td>
<td></td>
</tr>
<tr>
<td>3.4 Net Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>350,432,687</td>
<td>257,274,716</td>
<td>494,022,865</td>
<td>14,384,261</td>
<td>360,482,892</td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>353,639,230</td>
<td>263,493,146</td>
<td>500,137,190</td>
<td>15,296,898</td>
<td>367,565,215</td>
<td></td>
</tr>
<tr>
<td>HEALTH OUTCOMES (E) : EDSS-DYA = Normalized EDSS-Disability-Years-Avoided = $E_{EDSS-QALY}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5 Total EDSS-DYA</td>
<td>#</td>
<td>761</td>
<td>761</td>
<td>761</td>
<td>82</td>
<td>839</td>
<td></td>
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<tr>
<td>3.6 Expected EDSS-DYA</td>
<td>EDSS- DYA</td>
<td>0.84</td>
<td>0.84</td>
<td>0.84</td>
<td>0.91</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>per PwMS Treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COST/EFFECTIVENESS RATIOS : C/E $E_{EDSS-QALY}$ (current dollars)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.7 Cost/EDSS-DYA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>460812</td>
<td>338,215</td>
<td>649,446</td>
<td>174,940</td>
<td>429,831</td>
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</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>464896</td>
<td>346,390</td>
<td>657,484</td>
<td>186,039</td>
<td>438,276</td>
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</tr>
<tr>
<td>(b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Treatment Costs</td>
<td>$</td>
<td>18071,1669</td>
<td>135,533,752</td>
<td>225,335,699</td>
<td>10,142,872</td>
<td>190,854,541</td>
<td></td>
</tr>
<tr>
<td>3.2 HC Cost Foregone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>1445945</td>
<td>2,891,890</td>
<td>2,758,133</td>
<td>643,498</td>
<td>3,477,995</td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>447462</td>
<td>892,137</td>
<td>857,528</td>
<td>196,469</td>
<td>1,073,482</td>
<td></td>
</tr>
<tr>
<td>3.3 Net Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>179265724</td>
<td>132,641,862</td>
<td>222,577,567</td>
<td>9,499,374</td>
<td>187,376,546</td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>180264207</td>
<td>134,641,614</td>
<td>224,478,171</td>
<td>9,946,403</td>
<td>189,781,059</td>
<td></td>
</tr>
<tr>
<td>HEALTH OUTCOMES, PRESENT VALUES</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4 Total EDSS-DYA</td>
<td>EDSS-DYA</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>40</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>3.5 Expected EDSS-DYA</td>
<td></td>
<td>0.27</td>
<td>0.27</td>
<td>0.27</td>
<td>0.44</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>per PwMS Treated</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6 Cost/EDSS-DYA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) per utilizer</td>
<td>$</td>
<td>734935</td>
<td>543,791</td>
<td>912,500</td>
<td>234,800</td>
<td>668,115</td>
<td></td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
<td>$</td>
<td>739028</td>
<td>551,990</td>
<td>920,292</td>
<td>245,850</td>
<td>676,688</td>
<td></td>
</tr>
<tr>
<td>MS Onset Cohort, EDSS Progression Modelled Over 40 Years</td>
<td>Scenarios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Units</td>
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<td># 2</td>
<td># 3</td>
<td># 4</td>
<td># 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### (a) PROGRAM COSTS (C) (Current Canadian dollars)

#### 3.1 PwMS Treated
- $790

#### 3.2 Treatment Costs
- $281,149,453

#### 3.3 HC Cost Foregone
- $2,412,094
  - a) per utilizer: $5,779,398
  - b) per PwMS at Risk: $2,536,238

#### 3.4 Net Costs
- $257,021,959
  - a) per utilizer: $115,790,597
  - b) per PwMS at Risk: $123,839,190

### HEALTH OUTCOMES (E): EDSS-DYA = Normalized EDSS-Disability-Years-Avoided = E_{EDSS-QALY}

#### 3.5 Total EDSS-DYA
- 713

#### 3.6 Expected EDSS-DYA per PwMS Treated
- 0.90

### COST/EFFECTIVENESS RATIOS (C/E_{EDSS-QALY}) (current dollars)

#### 3.7 Cost/EDSS-DYA
- a) per utilizer: $360,517
- b) per PwMS at Risk: $386,252

### (b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET

#### 3.1 Treatment Costs
- $145,684,938

#### 3.2 HC Cost Foregone
- $8,344,098
  - a) per utilizer: $1,999,275
  - b) per PwMS at Risk: $871,867

#### 3.3 Net Costs
- $137,340,840
  - a) per utilizer: $143,685,662
  - b) per PwMS at Risk: $61,990,910

### HEALTH OUTCOMES, PRESENT VALUES

#### 3.4 Total EDSS-DYA
- $247

#### 3.5 Expected EDSS-DYA per PwMS Treated
- 0.31

### COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)

#### 3.6 Cost/EDSS-DYA
- a) per utilizer: $557,008
- b) per PwMS at Risk: $582,740

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### Table 5.3-2 COST/EFFECTIVENESS SCENARIO RESULTS FOR MALES (Scenarios # 6 to # 10)

<table>
<thead>
<tr>
<th>MS Onset Cohort, EDSS Progression Modelled Over 40 Years</th>
<th>Scenarios</th>
<th># 6</th>
<th># 7</th>
<th># 8</th>
<th># 9</th>
<th># 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) PROGRAM COSTS (C) (Current Canadian dollars)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 PwMS Treated $</td>
<td></td>
<td>790</td>
<td>790</td>
<td>790</td>
<td>790</td>
<td>790</td>
</tr>
<tr>
<td>3.2 Treatment Costs $</td>
<td></td>
<td>266,983,525</td>
<td>295,248,640</td>
<td>281,149,453</td>
<td>281,149,453</td>
<td>281,149,453</td>
</tr>
<tr>
<td>3.3 HC Cost Foregone $</td>
<td></td>
<td>12,015,943</td>
<td>36,169,340</td>
<td>24,126,394</td>
<td>24,126,394</td>
<td>48,252,788</td>
</tr>
<tr>
<td>a) per utilizer $</td>
<td></td>
<td>2,878,984</td>
<td>8,663,644</td>
<td>5,779,398</td>
<td>5,779,398</td>
<td>11,545,829</td>
</tr>
<tr>
<td>b) per PwMS at Risk $</td>
<td></td>
<td>254,967,582</td>
<td>259,079,300</td>
<td>257,023,059</td>
<td>257,023,059</td>
<td>232,896,665</td>
</tr>
<tr>
<td>3.4 Net Costs $</td>
<td></td>
<td>264,104,541</td>
<td>286,584,995</td>
<td>275,370,055</td>
<td>275,370,055</td>
<td>269,603,624</td>
</tr>
<tr>
<td>a) per utilizer $</td>
<td></td>
<td>259,248,640</td>
<td>295,248,640</td>
<td>281,149,453</td>
<td>281,149,453</td>
<td>281,149,453</td>
</tr>
<tr>
<td>b) per PwMS at Risk $</td>
<td></td>
<td>281,079,300</td>
<td>257,023,059</td>
<td>257,023,059</td>
<td>232,896,665</td>
<td>232,896,665</td>
</tr>
<tr>
<td>(b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Treatment Costs $</td>
<td></td>
<td>141,085,216</td>
<td>150,264,121</td>
<td>196,435,865</td>
<td>113,243,023</td>
<td>145,684,938</td>
</tr>
<tr>
<td>3.2 HC Cost Foregone $</td>
<td></td>
<td>4,146,375</td>
<td>12,521,582</td>
<td>13,705,840</td>
<td>5,407,580</td>
<td>16,688,195</td>
</tr>
<tr>
<td>a) per utilizer $</td>
<td></td>
<td>993,934</td>
<td>2,999,769</td>
<td>3,283,533</td>
<td>1,295,879</td>
<td>3,991,830</td>
</tr>
<tr>
<td>b) per PwMS at Risk $</td>
<td></td>
<td>136,938,843</td>
<td>137,742,539</td>
<td>182,730,025</td>
<td>107,835,442</td>
<td>128,996,743</td>
</tr>
<tr>
<td>3.3 Net Costs $</td>
<td></td>
<td>140,901,282</td>
<td>147,264,352</td>
<td>193,152,332</td>
<td>111,947,143</td>
<td>141,693,107</td>
</tr>
<tr>
<td>a) per utilizer $</td>
<td></td>
<td>140,901,282</td>
<td>147,264,352</td>
<td>193,152,332</td>
<td>111,947,143</td>
<td>141,693,107</td>
</tr>
<tr>
<td>(b) PROGRAM COSTS, PRESENT VALUE AT YEAR OF ONSET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4 Total EDSS-DYA $</td>
<td></td>
<td>123</td>
<td>370</td>
<td>405</td>
<td>160</td>
<td>247</td>
</tr>
<tr>
<td>3.5 Expected EDSS-DYA $</td>
<td></td>
<td>0.16</td>
<td>0.47</td>
<td>0.51</td>
<td>0.20</td>
<td>0.31</td>
</tr>
<tr>
<td>per PwMS Treated $</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6 Cost/EDSS-DYA $</td>
<td></td>
<td>$1,117,752</td>
<td>372,250</td>
<td>451,179</td>
<td>674,829</td>
<td>523,167</td>
</tr>
<tr>
<td>a) per utilizer $</td>
<td></td>
<td>1,117,752</td>
<td>372,250</td>
<td>451,179</td>
<td>674,829</td>
<td>523,167</td>
</tr>
<tr>
<td>b) per PwMS at Risk $</td>
<td></td>
<td>1,143,484</td>
<td>397,982</td>
<td>476,913</td>
<td>700,560</td>
<td>574,659</td>
</tr>
</tbody>
</table>

**HEALTH OUTCOMES (E)**

- EDSS-DYA = Normalized EDSS-Disability-Years-Avoided = \( E_{\text{EDSS-QALYs}} \)
- EDSS-QALYs

| 3.5 Total EDSS-DYA $                                |           | 355 | 1,069 | 713 | 713 | 713 |
| 3.6 Expected EDSS-DYA $                             |           | 0.45 | 1.35 | 0.90 | 0.90 | 0.90 |

**COST/EFFECTIVENESS RATIOS**

- \( C/E_{\text{EDSS-QALY}} \) (current dollars)

| 3.7 Cost/EDSS-DYA $                                  |           | 718,166 | 743,902 | 360,517 | 360,517 | 326,676 |
| a) per utilizer $                                    |           | 718,166 | 242,394 | 360,517 | 360,517 | 326,676 |
| b) per PwMS at Risk $                               |           | 743,902 | 386,252 | 386,252 | 378,163 |

**HEALTH OUTCOMES, PRESENT VALUES**

| 3.4 Total EDSS-DYA $                                |           | 123 | 370 | 405 | 160 | 247 |
| 3.5 Expected EDSS-DYA $                             |           | 0.16 | 0.47 | 0.51 | 0.20 | 0.31 |

**COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)**

<p>| 3.6 Cost/EDSS-DYA $                                  |           | $1,117,752 | 372,250 | 451,179 | 674,829 | 523,167 |
| a) per utilizer $                                    |           | 1,117,752 | 372,250 | 451,179 | 674,829 | 523,167 |
| b) per PwMS at Risk $                               |           | 1,143,484 | 397,982 | 476,913 | 700,560 | 574,659 |</p>
<table>
<thead>
<tr>
<th>Table 5.3-3 COST/EFFECTIVENESS SCENARIO RESULTS FOR MALES (Scenarios # 11 to # 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Onset Cohort,EDSS Progression Modelled Over 40 Years</td>
</tr>
<tr>
<td>Units</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>(a) PROGRAM COSTS (C) (Current Canadian dollars)</td>
</tr>
<tr>
<td>3.1 PwMS Treated</td>
</tr>
<tr>
<td>3.2 Treatment Costs</td>
</tr>
<tr>
<td>3.3 HC Cost Foregone</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>3.4 Net Costs</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>3.5 Total EDSS-DYA</td>
</tr>
<tr>
<td>3.6 Expected EDSS-DYA per PwMS Treated</td>
</tr>
<tr>
<td>COST/EFFECTIVENESS RATIOS : C/E_EDSS-QALY _ (current dollars)</td>
</tr>
<tr>
<td>3.7 Cost/EDSS-DYA</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>(b) PROGRAM COSTS, PRESENT VALUES AT YEAR OF ONSET</td>
</tr>
<tr>
<td>3.1 Treatment Costs</td>
</tr>
<tr>
<td>3.2 HC Cost Foregone</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>3.3 Net Costs</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>HEALTH OUTCOMES, PRESENT VALUES</td>
</tr>
<tr>
<td>3.4 Total EDSS-DYA</td>
</tr>
<tr>
<td>3.5 Expected EDSS-DYA per PwMS Treated</td>
</tr>
<tr>
<td>COST/EFFECTIVENESS RATIOS, PRESENT VALUES (of costs and health outcomes, at onset)</td>
</tr>
<tr>
<td>3.6 Cost/EDSS-DYA</td>
</tr>
<tr>
<td>a) per utilizer</td>
</tr>
<tr>
<td>b) per PwMS at Risk</td>
</tr>
<tr>
<td>CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730</td>
</tr>
</tbody>
</table>
3.5.2 Downward Revisions of Betaseron® C/E\textsubscript{nEDSS-DYA} Estimates from a Department of Health Perspective given 1) a More Complete Modelling of MS Natural History, 2) Higher EDSS Means for the Severely Disabled and 3) Adoption of a Societal Perspective

3.5.2.1 Foundations of C/E\textsubscript{nEDSS-DYA} Estimates Reported in Tables 5.2 and 5.3

Estimates of the cost-effectiveness of Betaseron® in slowing MS disability progression, presented in section 3.3 above, are based on (1) a model of MS disability progression which uses only one EDSS endpoint rather than multiple EDSS endpoints to characterize MS natural history progression, (2) mean EDSS data for 'mild' and 'severe' disability derived from MS clinic data rather than MS population data and (3) a 'public sector department of health' perspective rather than a 'societal' perspective for purposes of estimating costs foregone due to treatment.

The estimates in Tables 5.2 and 5.3 of Betaseron® C/E\textsubscript{nEDSS-DYA}, based on a department of health perspective, are biased upwards due in factors (1) and (2) just cited. Because the single EDSS=6 endpoint model does not adequately capture the timing and frequency distributions of MS disability progression in an MS onset cohort over the natural history of MS, estimates of treatment effects based on a single endpoint are biased downward compared to estimates based on models which use two or more cumulative probability distributions of EDSS endpoints to represent MS disability progression. This bias is demonstrated by Grenier's comparison of C/E\textsubscript{nEDSS-DYA} estimates based on (1) a single EDSS endpoint model and (2) a two EDSS endpoint model, for baseline Scenario #1 for females. Grenier's results, summarized below, suggest the order of magnitude of downward revisions to C/E\textsubscript{nEDSS-DYA} estimates in Tables 5.2 and 5.3 which flow from a more complete modelling of MS disability progression. (Grenier 1996a)

Grenier also notes that C/E\textsubscript{nEDSS-DYA} estimates in Tables 5.2 and 5.3 are based on EDSS means for 'mild' and 'severe' disability which originate from MS clinic data. Since very severely disabled PwMS who are bedridden at home or in an institution tend to be under-represented in MS clinic populations compared to the MS population at large, estimates based on MS clinic data will tend to be downward biased with respect to treatment effects and upward biased with respect to C/E ratios. An estimate of the order of magnitude of this bias on C/E\textsubscript{nEDSS-DYA} estimates is also given below, based on data recently collected by Grenier. (Grenier, 1996b)
The section concludes with a brief discussion of why $C/E_{nEDSS-DYA}$ estimates will be revised downward even further if the C/E analysis is conducted from a societal perspective rather than a department of health perspective. However, while further downward revisions of $C/E_{nEDSS-DYA}$ estimates are to flow from adoption of a societal perspective, no estimate is given of the order of magnitude of such a revision. It is judged that further research is required on precisely how Betaseron treatment impacts on MS-related societal costs before it is possible to estimate (1) societal costs foregone compared to department of health costs foregone due to Betaseron treatment, and (2) the size of further downward revisions of $C/E_{nEDSS-DYA}$ estimates which would flow from adoption of a societal perspective. Estimating societal costs foregone lies beyond the terms of reference of this study.

3.5.2.2 $C/E_{nEDSS-DYA}$ Estimates for Scenario #1 Based on (1) a Single EDSS Endpoint Model and (2) a Department of Health Perspective: A Review of Methods

Estimates in Tables 5.2 and 5.3 are based on the following methods, data and analytical perspective.

1. MS Natural History disability progression in an MS onset cohort is modelled using the cumulative probability of reaching a single endpoint EDSS=6 over the 40 year period following onset of MS symptoms. The analysis is stratified by females, males, rr and cp classifications of MS. Figures 2 - 3 above show these Natural History time paths of MS disability progression in an MS onset cohort of females and of males.

2. Based on RCT results Betaseron efficacy is modelled to delay the cumulative probability of reaching EDSS=6 by 15%. Figures 4 - 9 show both Natural History and Treatment time paths for disability progression to EDSS=6 given a 15% time delay due to treatment. Treatment is modelled to begin two years after onset of symptoms, following a definite diagnosis of MS, and is modelled to stop following an assessment of EDSS≥6 in two consecutive years.

3. Estimated Betaseron treatment effects within 1,000 person onset cohorts of females and males are depicted in Figures 4 - 9 as the areas between the Natural History time paths and the Treatment time paths of the cumulative probability of not reaching endpoint EDSS=6. The areas between the curves show the additional time spent in a “mild" disability state (EDSS<6) rather than “severe" disability state (EDSS≥6) as a consequence of treatment.
4. The total treatment effect within the 1,000 person onset cohorts over the 40 years following MS onset is measured as 'normalized EDSS-weighted-Disability-Years-Avoided', nEDSS-DYA. The EDSS (range 0 to 10) is divided by 10 to give a 'normalized' disability scale (range 0 - 1), designated nEDSS. nEDSS-DYA are estimated by weighting (multiplying) the additional time (person-years) spend in a 'mild' disability state instead of a 'severe' disability state by the difference in mean nEDSS scores for 'severe' and 'mild' disability states.

5. The analytical perspective adopted is that of a 'public sector department of health' (DoH). Estimated foregone costs due to treatment, from a DoH perspective, are the direct health care costs avoided because treated PwMS are expected to spend more time in a lower cost 'mild' disability state and less time in a higher cost 'severe' disability state.

6. C/E_{nEDSS-DYA} estimates for 'baseline' Scenario #1 in Tables 4.2 and 4.3, using the above methods and PwMS-at-risk cost perspective, are presented in abbreviate form in Table 5.4.

<table>
<thead>
<tr>
<th>Table 5.4 C/E_{nEDSS-DYA} Estimates for Scenario #1 Based on (1) a EDSS=6 Endpoint Model and (2) a Department of Health Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Tables 5.2-1 &amp; 5.3-1</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Males</td>
</tr>
</tbody>
</table>

3.5.2.3 Revised C/E_{nEDSS-DYA} Estimates for Scenario #1 Based on (1) a Two EDSS Endpoint Model and (2) a Department of Health Perspective

1. The use of a two-stage model of MS Natural History of disability progression, rather than a one-stage model, substantially increases the size of the estimated total treatment effect, and substantially reduces estimated C/E_{nEDSS-DYA} ratios. The use of both EDSS=3 and EDSS=6 as disability progression endpoints, together with EDSS means of 1.7 in interval 0≤EDSS≤2.5, 4.6 in interval 3≤EDSS≤5.5 and 6.35 in interval 6≤EDSS≤10, increases the estimated treatment effect E_{nEDSS-DYA} per female by 68% (from 0.843 to 1.416) before discounting, and by 92% (from 0.256 to 0.494) after discounting by 5%. (Source of EDSS means for intervals 0≤EDSS≤2.5 and 3≤EDSS≤5.5 is Grenier 1996b; source of EDSS mean for interval 6≤EDSS≤10 is DMSRU.) These revised estimates of treatment effect E_{nEDSS-DYA} reduce the size
of $C/E_{nEDSS-DYA}$ ratio estimates for Scenario #1 for rr females by 46% (undiscounted) and by 51% (discounted), as shown in Table 5.5.

| Table 5.5 Revised $C/E_{nEDSS-DYA}$ Estimates for Scenario #1 Based on (1) a EDSS=3 and EDSS=6 Endpoint Model and (2) a DoH Perspective |
|-------------------------------------------------|-----------------|-----------------|
| Females                                        | Undiscounted    | Discounted      |
|                                                | $248,765 (54% of Table 4) | $364,007 (49% of Table 4) |

The use of additional EDSS endpoints in modelling MS disability progression up to EDSS=6 would further increase measured treatment effects, but by much smaller amounts than the change produced by adopting a two endpoint model rather than one endpoint model. A model using multiple EDSS endpoints in the treatment range $0 \leq EDSS \leq 6$ increases measured benefits for several reasons. First, the use of multiple disability progression endpoints facilitates a more complete and accurate estimate of treatment effects which slow disability progression. Second, the use of multiple endpoints facilitates measurement of treatment effects which occur soon after treatment begins. And third, the use of multiple endpoints reduces the difference between undiscounted and discounted measures of treatment effects because treatment effects are captured sooner after treatment begin, thereby providing a more symmetrical present value analysis of treatment effects and treatment costs.

3.5.2.4 Revised $C/E_{nEDSS-DYA}$ Estimates for Scenario #1 Based on (1) a Two EDSS Endpoint Model, (2) Higher EDSS Means for the Most Severely Disabled, and (3) a Public Sector Department of Health Perspective

$C/E_{EDSS-DYA}$ estimates in Table 5 use EDSS means for 'mild' and 'severe' disability derived from DMSRU clinic data. Studies comparing MS clinic populations to representative MS populations find that very severely disabled PwMS, such as those who are bedridden at home or in long term care facilities, are under represented in MS clinics. Consequently mean EDSS scores for the DMSRU 'severe' disability group with EDSS $\geq 6$ are likely biased downward. Based on one recent study which found an EDSS mean of 7.3 compared to 6.35 in the DMSRU study group, this would result in underestimates of $E_{nEDSS-DYA}$ by 14% in females classified as rr. (Grenier, 1996b) The substitution of the 7.3 EDSS mean for the 6.35 EDSS mean reduces $C/E_{nEDSS-DYA}$ estimates from 54% to 47% of the undiscounted Table 4 Scenario #1 estimate for females, and from 49% to 44% of the discounted Table 5 estimate (Table 5.6).
Table 5.6 C/E\textsubscript{\textit{nEDSS-DYA}} Estimates for Scenario #1 Based on (1) a Two EDSS Endpoint Model, (2) Higher EDSS Means for ‘Severe’ Disability and (3) a Department of Health Perspective

<table>
<thead>
<tr>
<th></th>
<th>Undiscounted</th>
<th>Discounted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>$219,061 (47% of Table 5)</td>
<td>$325,760 (44% of Table 5)</td>
</tr>
</tbody>
</table>

As a consequence of using (1) a two stage rather than a one stage model of disability progression and (2) a higher EDSS mean for ‘severe’ disability, C/E\textsubscript{\textit{nEDSS-DYA}} estimates for Betaseron\textsuperscript{®} treatment of females classified as rr from a DoH perspective are revised downward by more than 50\%, from $463,072 to $219,061 in current dollars and from $737,205 to $325,760 after discounting both costs and treatment outcomes by 5\% to time of onset. (Table 5.6) These revised estimates for Scenario #1 are based only on data for females classified as rr. Comparable data for males are at present unavailable.

### 3.5.2.5 Towards Unbiased Estimates of Betaseron\textsuperscript{®} Treatment Effects Through Improved Modelling of MS Natural History

Grenier's comparison of the difference in C/E\textsubscript{\textit{nEDSS-DYA}} estimates which flow from a one EDSS=6 endpoint model compared with a two EDSS=3 and EDSS=6 endpoint model of MS disability progression suggests the order of magnitude of downward revisions which should be applied to the C/E\textsubscript{\textit{nEDSS-DYA}} estimates in Tables 5.2 and 5.3. That comparison illustrates that the size of estimated treatment effects and of estimated C/E ratios is quite sensitive to how MS natural history progression is modelled for purposes of assessing the therapeutic and economic consequences of new therapies. It is clear that such evaluation studies would benefit from the development of more complete and sensitive models of MS progression.

The size of the downward revisions to C/E\textsubscript{\textit{nEDSS-DYA}} estimates in Tables 5.2 and 5.3 suggested by Grenier's two EDSS endpoint analysis are themselves upward biased, for the same reasons that estimates based on a single EDSS endpoint are downward biased. This bias would be reduced by extending the analysis from a two EDSS endpoint model (which covers the range 0\leq EDSS\leq 6) to a three EDSS endpoint, which covers the range, say, 0\leq EDSS\leq 7.5. Estimates of E\textsubscript{\textit{nEDSS-DYA}} following from a three EDSS endpoint model (e.g., EDSS=3, EDSS=6, EDSS=7.5) will be lower than estimates based on a two EDSS endpoint model (EDSS=3, EDSS=6) because estimates of E\textsubscript{\textit{nEDSS-DYA}} due to slower MS disability progression to and beyond EDSS=6 will be more...
accurately (and conservatively) estimated in the three endpoint model. The further development of multi-endpoint models used to represent MS disability progression over the natural history of MS will yield even better estimates of treatment consequences.

3.5.2.6 Revised C/E\textsubscript{nEDSS-DYA} Estimates for Scenario #1 Based on (1) a Two EDSS Endpoint Model, (2) a Higher EDSS Mean for the Most Severely Disabled, and (3) Adoption of a Societal Perspective

Adoption of a broad societal perspective for purposes of analysing the C/E of Betaseron\textsuperscript{®} in MS, instead of a relatively narrow public sector department of health perspective, may substantially increase the size of estimated costs forgone due to treatment, thereby reducing the size of both estimated Betaseron\textsuperscript{®} net program costs and C/E ratios. The impact may be substantial because recent MS burden-of-illness studies find that private sector indirect costs borne by PwMS and their principal caregivers are the most large component of full societal costs, which are large relative to department of health direct health care costs. (Whetten-Goldstein et al, 1996; Holmes et al, 1996; McGown and MCWhinnie, 1995; Grenier, 1996b; Versieck et al, 1996a, 1996b) Such indirect costs are ignored when a narrower DoH perspective is adopted. These indirect costs reflect MS-related foregone earnings opportunities of PwMS and their principal caregivers. Foregone earnings arise from higher unemployment rates, more work-days-lost and lost career opportunities which are related to the onset, severity and progression of MS symptoms and disabilities. Since the cumulative probability of being employment, and of increased work-days-lost for those who continue to be employed, rises relatively rapidly following onset of MS symptoms there appears to be considerable potential for identifying relatively large foregone societal costs as a consequence of MS therapies which reduce the frequency and severity of MS symptoms and which delay the progression of MS disabilities and foregone earnings.

The extent to which estimated Betaseron\textsuperscript{®} net treatment costs and C/E\textsubscript{nEDSS-DYA} ratios would be reduced as a consequence of adopting a societal perspective, instead of a DoH perspective, is at present unknown and requires further research, which goes beyond the scope of this study. Besides the necessary data detailing MS burden of illness from a societal perspective which is becoming available from various studies, additional information is needed on the extent to which Betaseron\textsuperscript{®} treatment impacts on the cumulative probability of unemployment, work-days-lost and career opportunities foregone by PwMS and their principal caregivers.

One may conclude with confidence that the adoption of a societal perspective will yield lower C/E estimates than those which flow from comparable analyses based on a narrower analytical
perspective. However, further research is needed to quantify the extent to which current $C/E_{n\text{EDSS\text{-}DYA}}$ estimates for Scenario #1 suggested in Tables 5.4 and 5.5 will be revised downward still further as a result adopting a societal perspective rather than from a public sector department of health perspective.

### 3.5.2.7 Overview of Downward Revisions to $C/E_{n\text{EDSS\text{-}DYA}}$

#### Estimates for Betaseron® in MS

Table 5.7 summarizes the various downward revisions of $C/E_{n\text{EDSS\text{-}DYA}}$ estimates for females with MS classified as relapsing-remitting, based on Scenario #1 assumptions, reported in Table 5.2.

<table>
<thead>
<tr>
<th>Table 5.7: Summary of Downward Revisions to $C/E_{n\text{EDSS\text{-}DYA}}$ Estimates for Scenario #1, Females Classified as Relapsing-Remitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tables</td>
</tr>
<tr>
<td>4.2 Reference Estimate (100%)</td>
</tr>
<tr>
<td>4.5</td>
</tr>
<tr>
<td>4.6</td>
</tr>
<tr>
<td>4.7</td>
</tr>
</tbody>
</table>

Downward revisions to $C/E_{n\text{EDSS\text{-}DYA}}$ estimates for Scenarios #2 - #15, presented in Table 5.2 for females and in Table 5.3 for males, are expected to be of the same order of magnitude as those for Scenario #1 for females, i.e., by about 50%. Further research is required to produce estimates of appropriate downward revisions for each of the 15 Scenarios analysed in Table 5 based on a more complete modelling of MS disability progression and adoption of a broader societal perspective.
3.5.3 Commentary on Program Costs (C) and Health Outcomes (E) of C/E Results for Scenarios #1 - #15, Tables 5.2 & 5.3

3.5.3.1 Commentary

Program Costs (C)
“Betaseron® treatment program” costs vary directly with the number of persons treated and the costs per PwMS treated. Those Scenarios having 1) a higher proportion of PwMS at risk who are eligible for treatment, 2) a higher proportion of persons eligible for treatment who start treatment, and 3) a higher compliance rate, have a higher proportion of each 1,000 person onset cohort who are treated over the 40 years following onset. While the number of PwMS treated declines annually as cumulative mortality rises in the years following onset, cumulative mortality itself does not enter as a variable within the spreadsheet model. At present it is not known whether Betaseron® treatment alters cumulative mortality.

Public sector health care “costs foregone” due to treatment, within the spreadsheet model, vary directly with the size of treatment effects which reduce the rate of EDSS disability progression. Slower progression expands the time spent in 'mild' (lower cost) disability states and contracts the time spent in 'severe' (high cost) disability states. Costs forgone will also vary directly with the absolute size of the difference between health care costs per PwMS per year in 'severe" versus 'mild' disability states.

This difference will be a function of the absolute size of health care costs, which varies across jurisdictions, and the gradient of health care costs relative to disability severity, which also varies across jurisdictions. Total health care costs foregone for a given Scenario S_i are estimated by subtracting 1) total health care costs (exclusive of direct treatment costs) incurred by a 1,000 person onset cohort, given a Betaseron® treatment effect size of T_i, from 2), total health care costs in the absence of Betaseron® treatment, where disability progression follows the MS natural history path.

Because annual public sector health care costs per PwMS in Nova Scotia are small relative to Betaseron® direct treatment costs of $16,685 per PwMS per year (and the cost difference between ‘severe’ and ‘mild’ disability costs are also small by comparison) the subtraction of estimated costs foregone from direct treatment costs reduces total program costs by less than 1% in baseline Scenario #1. Foregone costs are also relatively small because they enter the spreadsheet analysis only in those years where additional time is spent in a 'mild' disability state instead of a 'severe' disability state. This time corresponds to the area between the MS progression “natural
history" path and the "treatment" path in Figures 4 - 9. Because the cumulative probability of reaching endpoint EDSS $\geq 6$ (‘severe' disability) progresses slowly from time of onset, health care costs foregone are experienced in full only many years after treatment begins. The relative size of health costs foregone to direct treatment costs is less in onset cohorts of PwMS classified as relapsing-remitting (rr) compared to onset cohorts of PwMS classified as chronic progressive (cp) because the cumulative probability of progression to EDSS $\geq 6$ is much lower for rr than for cp. Application of present value calculations at time of onset serve to reduce further the importance of health care costs foregone relative to Betaseron® direct treatment costs. The consequence of present value calculations on the relative size of foregone costs is greater in onset cohorts classified as rr, versus cp, because of the slower rate of disability progression in rr.

Net Betaseron® treatment program costs, which equal direct treatment costs minus public sector direct health care costs foregone in this analysis, are estimated to be 98% or more of direct treatment costs in most scenarios.

**Health Outcomes (E)**

Health outcomes due to Betaseron® treatment are measured as (normalized) EDSS-weighted-disability-years avoided, nEDSS-DYA. Health outcomes are also expressed relative to the burden of nEDSS-disability-years experience over the natural history of MS.

In baseline Scenario #1 (Table 5.2), nEDSS-DYA for females, given a 15% treatment effect, are estimated to total 761 (713) over the 40 year history of an onset cohort of 1,000 females (males). Dividing by 910 females (790 males) treated to compute the expected treatment benefit per person in the MS onset cohort classified as rr, gives an estimated lifetime reduction of 0.84 nEDSS-DYA per female, and 0.90 per male. This represents about a 6% reduction in total nEDSS-disability-years expected in the absence of Betaseron® treatment.

When these treatment health outcomes are expressed as present values at time of onset of MS symptoms, using a 5% discount rate, $E_{nEDSS-DYA}$ per female falls from 0.84 to 0.27 (-68%), and for males falls from 0.90 to 0.31 (-66%).

**C/E Ratios for Betaseron® Treatment Programs**

C/E ratios for Betaseron® treatment programs are computed by dividing net program costs by health outcomes. C/E ratios computed on a ‘cost per utilizer' basis do not differ much from those computed on a 'cost per PwMS at risk' basis, even though ‘Medicare' costs per utilizer are much higher than costs per PwMS at risk. This is because the absolute size of Betaseron® direct treatment costs, dominates even substantial variations in health care costs foregone. For
purposes of program evaluation, calculation of foregone costs on a ‘per PwMS at risk’ basis appear to be the appropriate method.

C/E ratios in Table 2, Part (a), are reported in current dollars, while C/E ratios in Table 2, Part (b), are reported in terms of present values at time of onset of MS symptoms. C/E ratios, expressed as present values at time of MS onset, are computed by discounting both costs and health outcomes streams from onset to 40 years after onset. When treatment costs, foregone costs, and health outcomes are spread over many years it is appropriate to report economic costs and consequences in both current dollars and in 'present value equivalents' at a particular point in time. Analytical symmetry requires that health outcomes be treated similarly, being reported in both natural units (eg, premature deaths avoided) and in 'present value equivalents' at the same point in time used for costs. (Drummond et al, 1987, Brooks, 1995)

**Scenario #1**
The C/E ratio for Scenario #1 is **$463,072** CDN per nEDSS-DYA for females and **$386,252** for males (based on current dollars, PwMS at risk basis, all rr PwMS eligible for treatment following definite diagnosis, with treatment discontinued once EDSS=6 is reached). These same C/E results when expressed on a present value basis at time of MS onset are even higher, being **$737,205** for females and **$582,740** for males. C/E ratios computed on a cost per utilizer basis are marginally lower.

C/E ratios expressed as present values, rather than in current dollars, are 44% higher for females and 34% higher for males with MS. C/E values expressed as present values are substantially greater than C/E values expressed in current dollars because Betaseron treatment costs are modelled to begin soon after onset of MS symptoms (in year 3) whereas treatment benefits, modelled as delayed onset of ‘severe' disability, typically occur many years later as MS disability proceeds along its natural history path, adjusted for treatment effect.

**Scenarios # 2 - Scenario #5**
- are similar to baseline Scenario #1 except for variations in factors such as compliance rates, treatment eligibility criteria, antibody effects, and user copayment fees. These scenarios differ from baseline Scenario #1 (or another scenario) by varying only one factor at a time. This is done to increase comparability, not because Scenario #1 is considered to be the “most realistic” scenario. Because differences in C/E results across scenarios are almost proportional, readers can, using pencil and paper, 'mix and match' different scenario results and thereby generate reasonable estimates for other scenarios of interest to them.
Compliance Rates After Five Years - Scenario #2
- is identical to baseline Scenario #1 except that PwMS compliance with Betaseron® treatment regimen is 45%, rather than 100%. Program costs fall nearly proportionately when expressed in either current dollars or present values. C/E ratios, however, change very little. This reflects the fact that treatment costs and treatment health benefits fall jointly, leaving the C/E ratio almost the same as in Scenario #1. Similar comparative results are observed for Scenario #3 where compliance is modelled at 20%, rather than 100%, five years after treatment commences.

Antibody Development - Scenario #4
- models antibody buildup in 40% of PwMS receiving treatment by five years after treatment begins. After the fifth year of treatment only 60% of patients who began treatment continue receiving treatment in this scenario. Relative to Scenario #1, total program costs fall by about 30% in current dollars and by 25% expressed as present values. C/E ratios rise by about 11% in current dollars and by 16% in present values.

User Co-payment Fees - Scenario #5
- is similar to Scenario #2, with the addition of a 20% user co-payment charge for Betaseron® costs. Demand for treatment falls by 20%, given a price elasticity of unity, with similar declines in total program expenses. Total health benefits also decline proportionally since fewer PwMS receive treatment. C/E ratios decline slightly.

3.5.3.2 Sensitivity Analyses

Scenarios #6 - #13
- explore the consequences of major changes in certain key variables such as treatment efficacy size, discount rates, health care costs, the price of Betaseron®, and continuation of treatment indefinitely.

Treatment Efficacy - Scenario #6
- reduces the size of the treatment effect on MS disability by 50%, from 15% to 7.5% slower rate of progression, while Scenario #7 increases this treatment effect by 50%, from 15% to 22.5%. In all other respects these scenarios are identical to Scenario #1. Predictably, total nEDSS-DYA double in Scenario #6 and fall by 50% in Scenario #7, while the C/E ratio rose by 94% in Scenario #6 and fell by 32% in Scenario #7.

Discount Rates - Scenario #8
- reduces the discount rate to 2.5% compared to the 5% rate in Scenario #1, while
Scenario #9
- increases the discount rate by 50% to 7.5%. In each scenario the undiscounted C/E ratio in “current dollars” is equivalent to using a zero discount rate. In Scenario #9 the present value of program costs for females increases by 39%, relative to Scenario #1, while the present value of health outcomes increases by 67% from 284 nEDSS-DYA to 475. The much greater increase in the present value of health outcomes, compared to health costs, reflects the preventive nature of Betaseron® treatment, where treatment costs are incurred immediately and treatment benefits accrue further in the future. As a consequence of the different time paths of program treatment costs and program health benefits, the Scenario #8 reduction in discount rate produces a 17% fall in the C/E ratio, expressed as present values at time of MS onset, from $737,205 to $586,292. Similar changes, but in the opposite direction, are found in Scenario #9 where the discount rate is raised from 5% to 7.5%.

Public Sector Health Care Costs - Scenario #10
- doubles health care costs per year per PwMS (exclusive of Betaseron® direct treatment costs) while Scenario #11 reduces these costs by 50%, both relative to Scenario #1. As a consequence, health care costs foregone double in Scenario #11, but net program costs decrease by only 2%. C/E ratios for Scenario #10 change only marginally. Similar effects, again in the opposite direction, are observed in Scenario #11 where health care costs are cut in half.

The Price of Betaseron® - Scenario #12
- has the price of Betaseron® fall by 25%, from $16,685 per year per PwMS treated to $12,513. Program direct treatment costs fall proportionately and net program costs fall slightly more than proportionately. Health outcomes are unaltered, so C/E ratios for females fall 25% from $463,072 to $346,390 in current dollars, and fall 25% from $737,205 to $551,990 expressed in present values.

Continuation of Treatment Indefinitely - Scenario #13
- differs from Scenario #1 in that treatment continues indefinitely, rather than being discontinued after a PwMS is assessed as EDSS≥6 in two consecutive years. Net program costs for females increase by 20% as a consequence, while the C/E ratio increases by 23%.

Treatment of Only PwMS Classified as Progressive from Onset - Scenario #14
- assumes that only PwMS classified as having a progressive from of MS as onset are treated, in contrast to Scenarios #1 - #13 which assume that only PwMS classified as relapsing-remitting at onset are treated. The estimated C/E_{nEDSS-DYA} ratio for Scenario #14 for females in present value
terms is $245,850, which is only a third of the comparable estimate for Scenario #1 of $737,205. The very large reduction in estimated C/E\textsubscript{nedSS-DYA} reflects the much more rapid disability progression of progressive forms of MS, which mean the E\textsubscript{nedSS-DYA} is larger and is realized sooner after onset compared to the treatment of relapsing-remitting forms of MS.

**Treatment of Both PwMS Classified as Relapsing-Remitting and Progressive from Onset Scenario #15**

- combines Scenario #1 and Scenario #14 to estimate treatment effects assuming that PwMS classified as either rr or cp at onset are eligible for Betaseron\textsuperscript{®} treatment from time of definite diagnosis until an assessment of EDSS=6 in two successive years. Estimated C/E\textsubscript{nedSS-DYA} ratios are a blend of those for Scenarios #1 and #14, and reflect the relative frequencies of both gender and MS classifications.

The foregoing scenarios simulated substantial changes in the size of key variables in the C/E model. The changes observed in total program costs, health outcomes and C/E ratios (compared to Scenario #1, or another relevant baseline) were in the expected direction and were roughly proportional to the size of change in the key variable. This indicates that the C/E spreadsheet model is internally consistent.

### 3.5.4 C/E Analysis Scope and Limitations

**MS natural history** is modelled very simply relative to the real complexity of MS natural history. The model presently focuses on the two major MS classifications, relapsing-remitting and chronic progressive (bout onset and primary progressive), with analyses of natural history progression based on classification at time of onset. Further development of the natural history module will take advantage of additional detail contained in the Swedish MS database. Other modelling approaches which include transitions from relapsing-remitting (bout onset) to relapsing-progressive (secondary progressive) are of interest for purposes of refining estimates of treatment health outcomes and for purposes of developing drug benefit eligibility criteria.

It is appropriate to broaden health outcomes measures included in the MS natural history model beyond EDSS measures, which focus heavily on ambulation. However, prospective longitudinal data describing MS progression using more comprehensive health status measures, comparable to the Swedish 25 year MS onset cohort data which characterizes MS natural history progression using repeat measures of EDSS, are simply not available at this time. Until such data are available, there will be benefits derived from research which identifies stable relationships
between EDSS measures of MS progression and other health status measures encompassing a broader range of health dimensions. A modest step in this direction is presented in Chapter IV.

**Treatment Efficacy** in slowing MS progression, when measured using the EDSS, is subject to various problems of interpretation. RCT data show that mean time to progression by one EDSS point is delayed by about 15% in the 8MIU Betaseron treatment group compared to the placebo group, among PwMS classified as rr and with EDSS<6 when recruited to the RCT. The precise interpretation of this efficacy effect is clouded, however, by the EDSS itself. A one point progression may imply a different order of magnitude of increases in the true burden of illness, depending upon where one happens to be on the EDSS. Descriptions of the MS neurologic and disability states represented on the EDSS (Appendix 1, Chapter III) suggest that progression by one EDSS point within the 'mild' disability range up to EDSS 5.5 involves a significantly smaller increase in the burden of illness than does progression by one EDSS point within the 'severe' disability range from EDSS=6 to EDSS=10, death related to MS.⁷

Within the C/E spreadsheet model Betaseron treatment effects which slow MS disability progression occur only within the 'mild' disability range, and are manifested by extension of time spend in the EDSS<6 range. As currently modelled, no additional treatment benefits are experienced in the 'severe' disability range EDSS≥6, even though treatment continues. This biases downward estimates of total health outcomes (E), given the plausibility of Betaseron treatment effects within the 'severe' disability range, and biases upwards C/E ratios. The size of this bias is limited, however, since within the spreadsheet model treatment is discontinued six years after a PwMS reaches EDSS≥6.

**Direct Treatment Costs** used in the C/E analysis are based on a unit price approved for Betaseron in 1995 by Canada Department of Health, Patented Medicines Price Review Board. This price was used throughout the 40 year MS natural history analysis. In fact, the price of Betaseron is likely to fall in the future for various reasons, including improved production methods, competition from other drugs being developed for MS, and the expiration of patent

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⁷ The relatively small number of PwMS who completed the ‘EDSS progression’ component of the Betaseron RCT precludes analysis of whether time to progression by one EDSS point was related to EDSS starting point, within the range EDSS<6. While at present there is no evidence that Betaseron treatment effects, demonstrated for PwMS classified as rr and EDSS<6, will also be demonstrated for EDSS≥6 and for PwMS in other classifications, it is plausible that this may be demonstrated in future. Such evidence is needed to inform insurance benefits policy and MS management decisions regarding eligibility for Betaseron treatment and termination of treatment.
rights followed by entry of generic product competitors. Sensitivity analysis (Scenario #13) demonstrated that C/E results are very sensitive to changes in direct treatment costs, since these dominate foregone health care costs in our analyses.

**Foregone Costs** in the C/E analyses were restricted to public sector direct health care costs (exclusive of direct treatment costs). This captures only part of foregone costs expected to be associated with treatments which slow MS progression. Not included in this C/E study are the costs of other public sector services provided to persons and families with MS and private sector costs, both direct (eg private sector health care costs) and indirect (foregone earnings due to MS-related reduced labour force participation and increased work-days lost), borne by persons and families with MS. In addition there are income support payments which, while not strictly economic costs, are relevant to cash-strapped governments.

Use of a broader definition of MS-related costs in the C/E analysis would broaden this study' evaluation perspective from that of I) pharmacare program managers and/or ii) 'Medicare' program managers within provincial departments of health, to iii) provincial departments of health managers and/or iv) provincial government mangers and/or v) persons with MS, their families, MS-related NGOs and citizens at large in the private sector. As costs included in the analysis are broadened toward an all encompassing societal perspective this will increase the size of foregone costs associated with effective MS treatments, which will in turn reduce net treatment costs (direct treatment costs minus foregone costs), and drive down both total net program costs and C/E ratios.

The definitive study of the true economic burden of MS has yet to be done, but available evidence suggests that public sector direct health care costs, used in this study, comprise perhaps half of the full direct and indirect economic costs of MS. (Jonsson, Abt, Veterans, Manitoba, McGown)

If public sector direct health care costs represent, say, 50% of full economic costs, and if other costs foregone due to reduced MS progression are proportional to those for public sector direct health care costs, then foregone costs would about double. In many C/E analyses a doubling of foregone costs radically alters both total net program costs and the program C/E ratio. In the present analysis, however, because Betaseron® direct treatment costs are so very large relative to estimates of public sector health care foregone costs foregone, a doubling or tripling of estimated costs foregone costs (e.g., as a consequence of adopting of a broader societal perspective which encompasses all public and private sector costs related to MS) produces only a comparatively small reduction in both Betaseron® net program costs and C/E ratios.
3.5.5 Generalizability of C/E Results

**MS Disease Progression** is apparently similar in MS populations throughout the world, so the MS natural history module based on a Swedish MS onset cohort followed prospectively for 25 years should be descriptive of MS progression generally.

**MS Prevalence** varies geographically, increasing with latitude for reasons unknown, reflecting migration patterns of genetically susceptible sub-populations and many other factors as yet poorly understood. Analyses of the therapeutic effects of Betaseron® are presented in this study in the context of hypothetical MS onset cohorts, for 1,000 females and for 1,000 males, using 25 year MS natural history data from Sweden, projected to 40 years. Scenario results reported in this Betaseron® evaluation study may be adapted, using back-of-the-envelop methods, to generate estimates of total Betaseron® program costs in a particular jurisdiction, using estimated MS prevalence in that jurisdiction. C/E ratios should be independent of MS prevalence.

**RCT Evidence** on Betaseron® treatment efficacy is generalizable, subject to its inherent limitations. RCT evidence is available only for PwMS classified as relapsing remitting and having 'mild' disability (EDSS<6) when recruited to the RCT. However, many Scenarios analysed above include PwMS classified as 'chronic progressive' as eligible for Betaseron® treatment who, when treated, benefit from a 15% reduction in rate of progression similar to that found in the RCT. Such scenarios are clearly speculative.

**Direct Treatment Costs** for Betaseron® used in the C/E analyses are based on a maximum approved price. Actual prices may be lower for various political jurisdictions, or private sector health insurance companies, depending upon whether bilateral agreements are reached with the supplier of Betaseron® and other factors discussed above.

**Foregone Health Care Costs** in the C/E analyses are based on Nova Scotia public sector 'Medicare' program costs. C/E spreadsheet model scenarios demonstrate how other jurisdictions, with higher or lower health care costs, may estimate how C/E results in their jurisdictions will differ from those reported in this study. Adjustments may be made using ratios of interprovincial (or international) differences in health care costs. A forthcoming study of MS Health Care Costs in Nova Scotia provides further detail on relationships between annual health care costs of persons with MS, stratified by various clinical criteria. The annual health care costs of PwMS are also compared to those of Nova Scotia's population at large. (Brown *et al*, 1996)
3.5.6 C/E Results Relative to Other Health-Related C/E Studies

How do the results of this cost / effectiveness study of Betaseron® in MS compare to other health-related C/E study results? A recent study by Tengs et al, "Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness," provides such comparative data. (Tengs et al, 1995) Due care must be exercised in comparing study results. The studies surveyed applied various methods to both cost and health outcomes measurement. What is reported as a C/E ratio in one study may carry quite a different interpretation than a C/E ratio reported in another study, even though both are presented as studies of life-saving interventions. (Mason, Drummond, Torrance 1993) Readers are cautioned that studies reviewed by Tengs et al report C/E ratios in US dollars, whereas C/E ratios estimated for Betaseron® are in Canadian dollars. Current exchange rate are about $1.00 CDN = $0.72 US, or $1.39 CDN = $1.00 US.

Tengs' study reviews 'life-saving interventions' while Betaseron® treatment RCT outcome measures all relate to improvements in the quality of life of persons with MS and to reductions in disease activity, which analysts regard as an intermediate outcome rather than a final health outcome. No claims are made at present that Betaseron® treatment prevents or reduces premature mortality in MS. Nevertheless it is instructive to compare results of the current study with those assembled by Tengs et al.

'Normalized EDSS-weighted Disability-Years-Avoided', E_{nEDSS-DYA}, is the health outcome measure used in this C/E study of Betaseron®. One may choose to regard E_{nEDSS-DYA} as a crude 'quality of life year' (QALY) index because, like other QALYs, an nEDSS-weighted life-year is anchored at one end by nEDSS=0 representing good health and at the other end by nEDSS=1 representing death related to MS. However, since the EDSS was conceived as a categorical index useful in describing stages of MS progression (Schwartz, 1995a, 756), nEDSS-weighted Disability-Years-Avoided lack the desirable measurement properties found in recently developed QALY instruments. (Torrence 1982, 1987; Brooks 1986, 1991, 1995, 1996)

Tengs et al study ranks the cost/life-year-saved study results from lowest (i.e., cost saving interventions with C/E ≤ 0) to highest (i.e., with cost/life-year-saved in the millions of dollars for certain environmental control programs and inappropriate screening programs). C/E estimates for Betaseron®, expressed as C/E_{EDSS-DYA}, fall in the middle and upper parts of Tengs' rank-ordered C/E results, but are really not directly comparable to cost/life-year-saved outcome measures in any case. (See Appendix D which contains selected tables of C/E results reported by Tengs et al.)
## APPENDIX 1. Functional Systems (Kurtzke) - Code Sheet

### A. Pyramidal

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal signs without disability</td>
</tr>
<tr>
<td>2</td>
<td>Minimal disability</td>
</tr>
<tr>
<td>3</td>
<td>Mild or moderate paraparesis or hemiparesis; severe monoparesis</td>
</tr>
<tr>
<td>4</td>
<td>Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia</td>
</tr>
<tr>
<td>5</td>
<td>Paraplegia, hemiplegia or marked quadriparesis</td>
</tr>
<tr>
<td>6</td>
<td>Quadriplegia</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### B. Cerebellar

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal signs without disability</td>
</tr>
<tr>
<td>2</td>
<td>Mild ataxia</td>
</tr>
<tr>
<td>3</td>
<td>Moderate truncal or limb ataxia</td>
</tr>
<tr>
<td>4</td>
<td>Severe ataxia of all limbs</td>
</tr>
<tr>
<td>5</td>
<td>Unable to perform coordinated movements due to ataxia</td>
</tr>
<tr>
<td>6</td>
<td>Use “7” throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing</td>
</tr>
<tr>
<td>7</td>
<td>Use “7” throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### C. Brainstem

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Signs only</td>
</tr>
<tr>
<td>2</td>
<td>Moderate nystagmus or other mild disability</td>
</tr>
<tr>
<td>3</td>
<td>Severe nystagmus; marked extraocular weakness, or moderated</td>
</tr>
<tr>
<td>4</td>
<td>Marked dysarthria or other marked disability</td>
</tr>
<tr>
<td>5</td>
<td>Inability to swallow or speak</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### D. Sensory

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Vibration or figure-writing decrease only in one or two limbs</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in 3 or 4 limbs</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs</td>
</tr>
<tr>
<td>4</td>
<td>Marked decrease in touch or pain or proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive loss in more than two limbs</td>
</tr>
<tr>
<td>5</td>
<td>Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head</td>
</tr>
</tbody>
</table>

CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730
6 = Sensation essentially lost below the head
9 = Unknown

E. Bowel & Bladder
0 = Normal
1 = Mild urinary hesitancy, urgency or retention
2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
3 = Frequent urinary incontinence
4 = In need of almost constant catheterization
5 = Loss of bladder function
6 = Loss of bowel and bladder function
9 = Unknown

F. Visual (Optic)
0 = Normal
1 = Scotoma with visual acuity (corrected) better than 20/30
2 = Worse eye with scotoma with maximum visual acuity (corrected) of 20/30 to 20/59
3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximum visual acuity (corrected) of 20/80 to 20/99
4 = Worse eye with marked decrease of fields and maximum visual acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 = Worse eye with maximum visual acuity (corrected) less than 20/200; grade 4+ maximal acuity of better eye of 20/60 or less
6 = Grade 5+ maximal visual acuity of better eye of 20/80 or less
7 = Add after first digit for presence of temporal pallor
9 = Unknown

G. Mental (Cerebral)
0 = Normal
1 = Mood alteration only (does not effect DSS score)
2 = Mild decrease in mentation
3 = Moderate decrease in mentation
4 = Marked decrease in mentation (chronic brain syndrome, moderate)
5 = Dementia or chronic brain syndrome - severe or incompetent

O. Other
0 = None
1 = Any other neurological findings attributed to MS (specify)
9 = Unknown
Appendix 2: Expanded Disability Status Scale (Kurtzke) - Code Sheet

Note: DSS steps below refer to patients who are fully ambulatory, and the precise step is defined by the Functional System score(s). DSS steps from 5 up are defined by ability to ambulate, and usual equivalents in Functional System scores are provided.

<table>
<thead>
<tr>
<th>Score</th>
<th>Physical Manifestations</th>
<th>Usual FS Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>Normal neurological exam</td>
<td>all grade 0*</td>
</tr>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS*</td>
<td>one grade 1</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS*</td>
<td>more than one grade 1</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS</td>
<td>one grade 2, others 0 or 1</td>
</tr>
<tr>
<td>2.5</td>
<td>Minimal disability in two FS</td>
<td>two grade 2, others 0 or 1</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one FS, or mild disability in three or four FS though fully ambulatory</td>
<td>one grade 3, others 0 or 1</td>
</tr>
<tr>
<td>3.5</td>
<td>Fully ambulatory but with moderate disability in one FS</td>
<td>one grade 3, one or two grade 2, others 0 or 1</td>
</tr>
<tr>
<td></td>
<td>OR two grade 3, others 0 or 1</td>
<td>or one grade 4, others 0 or 1</td>
</tr>
<tr>
<td></td>
<td>OR five grade 2, others 0 or 1</td>
<td>OR combinations of lesser grades exceeding limits of previous steps</td>
</tr>
<tr>
<td>4.0</td>
<td>Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to work without aid or rest some 500 metres</td>
<td>one grade 4, others 0 or 1</td>
</tr>
<tr>
<td>4.5</td>
<td>Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; relatively severe disability; able to walk without aid or rest some 300 metres</td>
<td>OR combinations of lesser grades exceeding limits of previous steps</td>
</tr>
<tr>
<td>5.0</td>
<td>Ambulatory without aid or rest for some 200 metres; disability severe enough to impair full daily activities (eg. To work a full day without special provisions)</td>
<td>one grade 5, others 0 or 1</td>
</tr>
<tr>
<td>5.5</td>
<td>Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities</td>
<td>OR combinations of lesser grades exceeding limits of previous steps</td>
</tr>
<tr>
<td>6.0</td>
<td>Intermittent or constant assistance (cane, crutches, braces) required to walk about 100 metres without resting</td>
<td>combinations with more than two grade 3+</td>
</tr>
<tr>
<td>6.5</td>
<td>Constant bilateral assistance (canes, crutches, braces) required to walk about 20 metres without resting</td>
<td>combinations with more than two grade 3+</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk beyond about 5 metres even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day</td>
<td>combinations with more than one grade 4+</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer; wheels self but cannot carry on in standard wheelchair a full day; may require a motorized wheelchair</td>
<td>very rarely pyramidal grade 5 alone</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms</td>
<td>combinations, generally grade 4+ in several systems</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions</td>
<td>combinations, generally grade 4+ in several systems</td>
</tr>
<tr>
<td>9.0</td>
<td>Helpless bed patient; can communicate and eat</td>
<td>combinations, mostly grade 4+</td>
</tr>
<tr>
<td>9.5</td>
<td>Totally helpless bed patient; unable to communicate effectively or eat/swallow</td>
<td>combinations, almost all grade 4+</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes cerebral function grade 1

**NOTE:** DSS should not change by 1.0 steps unless there is a change in same direction of at least one step in at least one FS. Each step (eg. 3.0 to 3.5) is still part of prior scale equivalent (ie. 3). Progression from 3 to 3.5 should be equivalent to the old 3.
IV TOWARDS A COMPREHENSIVE ASSESSMENT OF BETASERON® IN MS

4.1 Broadening the Analytic Framework for Both Health Outcomes and Costs

Estimates of the cost/effectiveness of Betaseron® in slowing disability progression over the natural history of MS have been presented, using normalized EDSS-weighted Disability-Years-Avoided as a measure of effectiveness ($E_{\text{nedSS-DYA}}$). This measure of effectiveness is specific to MS and is subject to criticism on various technical grounds already noted. Data availability dictated the development of a C/E$_{\text{nedSS-DYA}}$ analysis for purposes of investigating the cost/effectiveness of Betaseron® in slowing disability progression. More comprehensive and sensitive clinical and economic assessments of MS therapies require more comprehensive health outcome measures with better measurement properties. The use of generic health status measures, in addition to MS-specific health status measures, in evaluations of MS therapies will enable sensible comparison of results within and across disease conditions.

A single comprehensive and satisfactory measure of the burden of MS-related illness may never be developed. The complexity of the disease, its many manifestations, and difficulties in agreeing upon appropriate weights for such a broad range of health domains and changes in health status, present major measurement challenges. While generic or global general purpose health indices may satisfactorily measure major changes in MS-related health status, they are not sensitive enough to capture all of the important treatment effects specific to MS.

Given the early age of MS onset, its protracted natural history, and low MS-related mortality, C/E analyses of MS treatment effects must focus on health-related quality of life (HRQoL) effects rather than on quantity of life effects. Such analyses require data which describe how HRQoL changes over the natural history of MS. HRQoL data, when used to weight the time spent in various health states experienced over the natural history of MS, provide a measure of quality adjusted life years (QALYs) over the natural history of MS. (Figure 1 above) QALYs combine quality of life and quantity of life measures in a single number. (Normalized) EDSS-weighted Disability-Years-Avoided, $E_{\text{nedSS-DYA}}$, were used in this study to estimate the health consequences of Betaseron® treatment effects on MS disability progression. $E_{\text{nedSS-DYA}}$ outcome measures were used for pragmatic reasons relating to data availability. A more broadly based HRQoL measure would have been employed if the requisite data were available.
4.2 Measuring Health Outcomes and Quality Adjusted Time in Neurologic Disease

Current clinical research and outcomes assessment in MS rely on disability measurements that are heavily influenced by ambulation, eg EDSS. This strategy may be insensitive to the clinical changes affected by pharmacotherapeutic or rehabilitative interventions, and also disregards symptoms that patients seem to consider most important. (Schwartz, 1995) A more comprehensive approach is needed for evaluating clinical interventions in terms of their impact on the symptoms of MS, side effects, parameters of exacerbation, and disease progression, while considering the patient's perspective. (Schwartz, 1995a)

Quality-adjusted-time methods developed originally for assessment of cancer and acquired immunodeficiency syndrome may be extended to assessments of chronic diseases in general, and neurologic diseases in particular. The extended Q-TWiST method yields an estimation of treatment trade-offs in terms of Quality-adjusted Time Without Symptoms and Toxicities (Q-TWiST). It is a quality-adjusted survival analysis designed to integrate quality-of-life considerations into the comparison of treatments being evaluated in randomized clinical trials. A patient's survival time is adjusted according to the quality of life experienced. (Schwartz, 1995a, p. 756) The method incorporates both negative outcomes of treatment (i.e., toxicities), and positive outcomes (under the umbrella of Q-TWiST, or time without symptoms of disease and toxic side effects due to treatment), and weights assessment scores using patient derived preference values.

This approach moves towards a comprehensive assessment of treatment effects in chronic progressive disease which are essentially preventative in nature, ie where positive treatment outcomes are measured in terms of arrested or reduced rates or disease progression, reduced disease activity, and net gains in quality-adjusted-time over the natural history of the disease. The measurement tasks appear to be tractable since the approach incorporates measures commonly used in MS. The following health status domains are proposed in a Q-TWiST approach to measuring treatment effects in MS:

1. Disability Progression (EDSS rates of change, ambulation)
2. Disease Activity (lesion rates of change, MRI)
3. Exacerbations (rates, intervals, severity)
4. Symptoms (fatigue, etc.)
5. Toxicity, Side Effects (infections, etc)
6. Work Disability (labour force participation, work-days lost)
7. Psychosocial Morbidity (SIP, MHI)

Development of methods to measure MS treatment outcomes which are more comprehensive, and which incorporate relative value weights of persons with MS, would set the stage for future cost / effectiveness assessments. C/E assessments based upon a more comprehensive health outcome measure, with better measurement properties, would represent a major advance over C/E\text{EDSS-DYA} assessments, with its relatively narrow focus on ambulation and its weak measurement properties.

4.3 Measuring Full Economic Costs and Transfer Payments

Studies of MS costs conducted in various centres demonstrate that MS direct health care costs are high relative to those of the population at large and that indirect costs to persons with MS and their families are also high. Until recently few studies were able to link direct treatment and related health care costs to MS-related indirect costs for a representative sample of PwMS or to link such data to MS clinical measures of MS progression. (Brown \textit{et al}, 1996) Notable is a study by Bengt Jonsson of MS costs in Sweden using administrative data from various public sector sources, which presents a broad picture of costs associated with MS health care services, social support services and income transfer payment. Transfer payments are not conventionally regarded as a cost, but are a budgetary item. Costs of social support services and transfer payments were found to be about the same size as direct health care costs. Low labour force participation and high work-days lost were also documented. (Jonsson, 1995)

A welcome addition to Canadian data relating to the full economic costs of MS is recent study by McGown and McWhinnie, sponsored by Berlex Canada Inc., "MS Patient Survey: Cost and Reimbursement of Treatment, The Cost of Multiple Sclerosis." (McGown and McWhinnie) Their mail questionnaire elicited responses from 4,412 persons with MS across Canada, identified through the cooperation of MS clinics. Results show that indirect costs associated with reduced employed and work-days lost are large, and dominate direct (public and private sector) health care costs (emergency room visits, hospital stays, physician visits and prescription drugs). Results also demonstrate that annual costs per person with MS increase markedly across MS classifications which serve as proxies for MS progression and disease severity, ie benign MS (BAS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). (See Table 5 below.) The McGown and McWhinnie study, and other MS costs studies underway, encompass a broad spectrum of MS-related costs. Such data will facilitate adoption of a societal perspective in future studies of MS therapies.

CCOHTA Report: Betaseron® Evaluation, Brown et al, Dalhousie University, 960730
A quick comparison of direct health care costs reported in McGown and McWhinnie's study with comparable data collected by Brown et al, "MS Health Care Costs in Nova Scotia: A Life-Cycle Population-Based Study," funded by Serono Canada Inc. and the Multiple Sclerosis Society of Canada indicates that these MS health care data are generally consistent with one another. If anything, the Canadian survey results are about 25% higher than annual health care costs of PwMS in Nova Scotia, derived from administrative data. Nova Scotia data include only public sector 'Medicare' program costs, whereas the Canadian survey collected data on all health care costs. Canadian MS survey results i) report annual pharmacare costs per PwMS of $958, slightly lower than those for PwMS over age 65 covered by Nova Scotia's Seniors Pharmacare program, ii) report substantially lower costs for physicians services of $386, compared to PwMS in Nova Scotia, and iii) report hospital costs of $2978 per PwMS which are about 25% higher than those for PwMS at risk in Nova Scotia. (Figures 10 and 11, from Brown et al, 1996) Overall, however, the same order of magnitude of health care costs per PwMS are found in the Canada-wide mail questionnaire study of McGown and McWhinnie and in the Nova Scotia study based on administrative data for major “Medicare” programs. Disparities in costs reported by these two studies may simple reflect differences in interprovincial health care costs and differences in MS management practices. Scenarios # 11 and #12, Chapter III, found that doubling or halving health care costs of PwMS had little effect on C/E_{EDSS-DYA} ratios, given Betaseron's high direct treatment costs.

Cost gradients associated with MS progression in the Nova Scotia data are consistent with those found in the McGown study. Figures 10 and 11 compare physicians services, hospital services, and Seniors Pharmacare health care costs for the DMSRU study group, other PwMS, and the Nova Scotia population, on a per utilizer and population-at-risk basis. Figures 12 and 13 show how total health care costs increase with age, on both a utilizer and population-at-risk basis.

McGown and McWhinnie's estimates of the overall economic impact of MS in Canada appear to be biased downward due to their use of very conservative MS prevalence rates, ie between 60/100,000 and 100/100,000. Various MS prevalence studies in Canada and North America find higher rates.
Table 5.8: Costs of Multiple Sclerosis, (annual $CDN per patient) Canadian MS Patient Survey, 1995

<table>
<thead>
<tr>
<th></th>
<th>Overall per Patient Cost</th>
<th>BMS</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost Output</td>
<td>$4,144</td>
<td>$594</td>
<td>$2,251</td>
<td>$7,459</td>
<td>$8,848</td>
</tr>
<tr>
<td>ER Visits</td>
<td>$75.80</td>
<td>$15.16</td>
<td>$83.38</td>
<td>$90.96</td>
<td>$90.96</td>
</tr>
<tr>
<td>Hospital Stays</td>
<td>$2,978.00</td>
<td>$397.00</td>
<td>$595.50</td>
<td>$3,176.00</td>
<td>$6,054.00</td>
</tr>
<tr>
<td>Physician Visits</td>
<td>$386.08</td>
<td>$114.90</td>
<td>$307.68</td>
<td>$547.76</td>
<td>$448.80</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>$958.20</td>
<td>$235.20</td>
<td>$732.72</td>
<td>$1,327.92</td>
<td>$1,126.80</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$8,542</strong></td>
<td><strong>$1,565</strong></td>
<td><strong>$3,971</strong></td>
<td><strong>$12,602</strong></td>
<td><strong>$16,569</strong></td>
</tr>
</tbody>
</table>

**Glossary:** BMS - benign MS; RRMS - relapsing remitting MS; SPMS - secondary progressive MS; PPMS - primary progressive MS.


Reproduced with permission.
Figure 10: Health Care Costs

DMSRU/Other MS/N.S. Utilizers - 1992/93

Cost / Utilizer / Year

- DMSRU: N = 487
- Other MS: N = 477
- Nova Scotia: N = 1735

Legend:
- Pharmacare
- Outpatient
- Inpatient
- Physician
Figure 11: Health Care Costs


<table>
<thead>
<tr>
<th></th>
<th>Cost / Person / Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSRU</td>
<td>$4,000</td>
</tr>
<tr>
<td>Other MS</td>
<td>$3,500</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>$3,000</td>
</tr>
</tbody>
</table>

- **Pharmacare**: Dark gray
- **Outpatient**: Light gray
- **Inpatient**: Black
- **Physician**: Light blue

Legend
Figure 12: Health Care Costs


Cost / Utilizer / Year

$12,000

$10,000

$8,000

$6,000

$4,000

$2,000

$0

Age Interval

20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84

DMSRU MS
Other MS
All MS
N.S. Pop’n

DMSRU N=1461
Other MS N=5208
All MS N=6669
N.S. N=2,449,246

30Oct95/DMSRU/ms_pv wk4, otherms wk4
Figure 13: Health Care Costs


Cost / Person / Year

$0, $1000, $2000, $3000, $4000, $5000, $6000, $7000

Age Interval


DMSRU N=533
All MS N=2528
Other MS N=1993
N.S. N=652,900
4.4 What We Can and Can't Measure: Measurement Limits in MS

4.4.1 Cautionary Note
Patients with MS often see the effects of their disease differently than their neurologists. The patients see the effect on their bodies and their life. This impacts primarily on their personal life, their hopes and their plans, their self confidence and self esteem, their families and their employment and future. Neurologists tend to see the disorder in terms of its measurable deficits, particularly measurements that can be quantifiable parts of the neurological examination. (Murray, 1995)

Traditionally, clinicians measured the extent and progression of the disease by the use of disability scales, particularly the Kurtzke DSS and the Extended Disability Status Scale (EDSS). The subcategories in the Kurtzke scale added a quantifiable aspect to the standard neurological examination. Such widely applied scales pay little attention to the effects on the person's daily life, relationships, employment and plans. Attempts are now being made to develop specific measurement scales for other important aspects of the MS patient's life and experience.

The EDSS is a reproducible but coarse measurement of impairment, the Incapacity Status Scale (ISS) measures disabilities, and the Environment Status Scale (ESS) measures handicaps. The EDSS can be used as a predictor of impairment of functional activities of daily living. The ESS includes actual work status, financial/economic status, personal residence/home, personal assistance required, transportation, community services and social activity, and provides some quantifiable measure of how the MS patient functions in society.

Aspects of MS that come under the umbrella of “psychosocial” can be found within a number of the scales used in MS, including those that primarily measure disability, because psychosocial status is affected by mobility, bladder and bowel control, sexual function, mood and mental change. Other effects of the disease are not as easily codified into scales and measures, because they are too nebulous, although important. There is no scale for the suffering experienced by the MS patient or their families, although aspects of this may be reflected in some other measurements. (Murray, 1995)

It may be that certain indicator scales such as the EDSS predict the change in other scales, and Kurtzke has argued that as patients progress as a group, all measurable indicators also progress.
However, in the future the assessment of cost-effectiveness of therapy may have to dissect out the differential affects on various aspects of the patient’s disease, life and experience.

In recent years scales have been developed to quantify the broader affects and experiences in MS including emotional and psychiatric disorders, fatigue, pain, coping behavior, cognitive change, quality of life, self-image, affects on relationships, employment and economic impact.

In the future it will be important to have a more global assessment of a new therapy on the many affects of MS on patients, and we believe that the tools and experience to do this are now available. (MS Management: Measurement in Multiple Sclerosis)

4.5 Converting $C/E_{nEDSS-DYA}$ Estimates To $C/U_{GENERIC-QALY}$ Guesstimates

Estimates of the $C/E$ of Betaseron® in MS produced in this report are expressed as cost per (normalized) EDSS-weighted Disability-Year-Avoided, or $C/E_{nEDSS-DYA}$, a crude type of quality-adjusted-life-year health outcome measure specific to multiple sclerosis. $C/E_{nEDSS-DYA}$ estimates are not directly comparable to $C/E$ or $C/U$ estimates which express costs relative to a more generic QALY outcome measures, $C/U_{GENERIC-QALY}$.

In order to compare the $C/E_{nEDSS-DYA}$ estimates for Betaseron® in MS with $C/U_{GENERIC-QALY}$ estimates reported for other therapies or programs research is needed which maps EDSS scores into generic HRQoL index scores. Conversion factors could then be used to transform $C/E_{nEDSS-DYA}$ estimates to $C/U_{GENERIC-QALY}$ estimates.

Research to develop conversion factors requires simultaneous collection of both EDSS scores and generic health index scores from the same representative sample of PwMS. EDSS scores for each step from 0 - 10 in the EDSS scale could then be mapped into one or more generic health indices, using means or other measures of central tendency. Equivalent generic health index scores could then be used instead of EDSS scores to estimate Betaseron® $C/E_{GENERIC-QALY}$ or $C/U_{GENERIC-QALY}$ in MS.

It was not feasible to engage in such ambitious data collection and conversion activities within the time and budget constraints of this study. However, given that some readers may prefer a rough estimate of the relationship between $C/E_{nEDSS-DYA}$ estimates and $C/U_{GENERIC-QALY}$ estimates
to no estimate at all, a set of rough estimates or ‘guesstimates’ is provided below. These are presented not as a substitute for appropriate data collection which will establish actual relationships between $C/E_{nEDSS-DYA}$ and $C/UGEneric-QALY$, but merely as a stop-gap means of increasing the comparability and generalizability of this study's estimates of Betaseron®'s $C/E_{nEDSS-DYA}$ in MS.

$$
(E_{nEDSS-DYA}) \times \text{(conversion factor } E) = U_{GENERIC-QALY}
$$

$$
(C/E_{nEDSS-DYA}) \times \text{(conversion factor } C/E) = C/UGEneric-QALY
$$

Estimation of a rough set of multiplicative “conversion factors” is facilitated by the straightforward method used to estimate $C/E_{nEDSS-DYA}$ in this study. Mean scores for PwMS in ‘mild’ and in 'severe' EDSS categories (EDSS<6 versus EDSS≥6) were computed from individual PwMS data contained in Dalhousie MS Research Unit (DMSRU) records, stratified by MS classification (rr, cp) and by gender. (Table 1 above) The mean scores for “mild” and “severe” disability were used, in conjunction with other data, to estimate both health outcomes ($E_{nEDSS-DYA}$) and health costs foregone. Thus only two points representing “mild” and “severe” disability on the EDSS need be mapped into a generic health index in order to roughly estimate “conversion factors” for the relationship, $(C/E_{nEDSS-DYA}) \times \text{(conversion factor } C/E) = C/UGEneric-QALY$.

Separate “conversion factors” are estimated for relapsing remitting (rr) and chronic progressive (cp) MS classifications. A weighted average of female and male mean EDSS scores for 'mild' and ‘severe' MS disability is used for purposes of roughly estimating “conversion factors” between $C/E_{nEDSS-DYA}$ and $C/UGEneric-QALY$ for PwMS in rr and cp classifications of MS.

The EuroQol EQ-5D Index of HRQoL is used to estimate “conversion factors.” The EQ-5D is perhaps the least complex of the many competing generic HRQoL indices. Its five health dimensions have been weighted, using time-trade-off methods, by relative values drawn from a representative sample of a general population (UK). (Williams 1995, Kind 1996, Dolan 1995, Brooks 1996) The EQ-5D questionnaire with its five health dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) and three health state levels per health dimension (no problems, some problems, extreme problems) is shown below.
Three Scenarios (A, B, C) are used to roughly map ‘mild' and ‘severe' EDSS mean scores into EuroQol index scores. Scenario A maps mean EDSS scores for “mild” and “severe” disability into the EQ-5D index using only the “mobility' dimension of the EuroQol index, while assigning “no problem” scores to each of the other 4 dimensions of the EQ-5D. Scenario A is meant to mimic within the EQ-5D the heavy weighting given to physical disability in the EDSS. Scenario A is expected to provide a lower-bound to estimates of “conversion factors”, given that only the narrow “mobility” disability attribute of the EDSS enters into the EQ-5D. This is done to contrast the size of “conversion factors” which emerges from Scenario A with “conversion factors” which emerge from Scenario B, which assigns some “moderate” health state levels, and Scenario C, which assigns some “extreme” health state levels, to the other 4 health dimensions of EQ-5D.

It should be noted that the (normalized) EDSS is a “disability” index comprising 20 discrete steps which run from 0 = good health to 1 = death related to MS. The EQ-5D is a HRQoL continuous “health” index which runs the other way from 1 = good health to 0 = death.

Table 6, “Mapping nEDSS Scores to EQ-5D Scores Using Simulated Health State Levels for Three Scenarios,” details the mapping of mean nEDSS scores for “mild” and “severe” disability, by MS classification and gender, into EQ-5D scores for Scenarios A, B and C.

Table 7. “Rough Estimates of (1) “Conversion Factor E” which Converts Health Outcomes “E” Measured as E_{nEDSS-DYA} to U_{EQ-5D-QALYs}, and (2) “Conversion Factor C/E” which Converts C/E_{nEDSS-DYA} to C/U_{EQ-5D-QALY}, using Simulated Health State Levels for Three Scenarios,” draws data from Table 6 to estimate two sets of “conversion factors”, i.e.,

(1) multiplicative “conversion factor E” expresses health outcomes (E) measured as E_{nEDSS-DYA} avoided, or (normalized) EDSS-weighted Disability-Years-Avoided, as U_{EQ-5D-QALYs} gained, or EQ-5D-weighted HRQoL-years-gained, and

(2) multiplicative “conversion factor C/E” which expresses C/E_{nEDSS-DYA} as C/U_{EQ-5D-QALY}.

Simulated health status scores for three scenarios provide a separate set of “conversion factor” estimates for rr and cp classifications of MS.
4.5.1 Results

SCENARIO A, has a “conversion factor E” of 1.25 for relapsing remitting MS. This suggests that nEDSS-DYA tends to understate treatment benefits by about 25% relative to treatment benefits measured by EQ-5D QALYs, or EuroQols, when only mobility dimensions of health status are taken into consideration. A “conversion factor E” of 1.71 for chronic progressive MS suggests that the size difference between $E_{nEDSS-DYA}$ and $EQ-5D$-QALYs estimates are related to both the range and severity of mobility disability measured by EDSS.

Inverting multiplicative “conversion factor E” gives “conversion factor C/E” estimates of 0.80 for rr and 0.58 for cp. This suggests that Betaseron© $C/E_{EQ-5D-QALY}$ estimates would be 20% to 38% lower than $C/E_{nEDSS-DYA}$ estimates, when only mobility dimensions of MS disability are taken into account.

SCENARIO B, which assigns some “moderate” health state levels to other health status dimensions of EQ-5D, yields a “conversion factor E” of 1.35 for rr and 1.79 for cp. This translates to a “conversion factor C/E” of 0.74 for rr and 0.56 for cp. Inclusion of some “moderate” adverse health outcomes for the four health status dimensions other than disability increases the difference between $C/E_{nEDSS-DYA}$ and $C/E_{EQ-5D-QALY}$ estimates, as expected.

SCENARIO C, which assigns some “severe” health status values to health status dimensions besides mobility, yields even higher “conversion factor E” estimates of 1.90 for rr and 2.62 for cp. These translate to a “conversion factor C/E” of 0.53 for rr and 0.38 for cp, a downward adjustment in the range of 47% to 62%.

4.5.2 Tentative Conclusions

The foregoing suggests that QALY estimates of Betaseron® treatment effectiveness (E) in slowing the rate of progression of MS disability over the natural history of MS, as measured by (normalized) EDSS-weighted-disability-years avoided, $E_{nEDSS-DYA}$, are conservative ‘QALY’ estimates of treatment effectiveness. Estimates of QALY treatment outcomes based upon a generic HRQoL index, $U_{GENERIC-QALYs}$, may be substantially larger.
Based on exploratory simulations which mapped EDSS scores to EQ-5D scores (Scenarios B and C), plausible values for multiplicative “conversion factor E” may fall in the range 1.33 to 2.00 for PwMS classified as rr, and in the range 1.8 to 2.6 for PwMS classified as cp. Estimates of treatment effectiveness measured by $U_{\text{GENERIC-QALY}}$ may therefore be substantially higher than estimates measured by $E_{n\text{EDSS-DYA}}$. If so, then estimates of $C/E$ measured by $C/U_{\text{GENERIC-QALY}}$ will also be substantially lower than estimates measured by $C/E_{n\text{EDSS-DYA}}$, perhaps in the range 0.75 to 0.50 for PwMS classified as rr, and perhaps in the range 0.55 to 0.40 for PwMS classified as cp.

These results are highly exploratory and should be interpreted with due caution. In particular it should be noted that the EQ-5D instrument was used together with (1) relative value weights derived in the UK from a representative sample of the general population and (2) the UK algorithm for placing raw EQ-5D scores on a EuroQol index which includes negative values (literally “worse than death”) for some very poor health states, to get EuroQol index scores for PwMS classified as “mild” or “severe” disabilities. Because the algorithm used to assign UK EuroQol index scores includes some relatively large negative scores, rather than constraining scores to be no worse than “0” (death), the exploratory estimates of “conversion factor E” and “conversion factor C/E” reported above are likely biased upward. This upward bias may be substantial.
Appendix 3: EQ-5D (second page)

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today. Do not tick more than one box in each group.

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-Care
I have no problems with self care
I have some problems washing and dressing myself
I am unable to wash or dress myself

Usual Activities (eg. work, study, housework, family or leisure)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
Table 6. Mapping EDSS Scores to EQ-5D Scores Using Simulated Health State Levels for Three Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>rr</th>
<th>cp</th>
<th>Mobility</th>
<th>Self-Care</th>
<th>Usual Activities</th>
<th>Pain / Discomfort</th>
<th>Anxiety / Depression</th>
<th>EuroQol-5D index score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.22</td>
<td>0.38</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>0.22</td>
<td>0.38</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>0.22</td>
<td>0.38</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Mild* Disability, EDSS<6

Scenario A, rr cp 0.63 0.68 3 1 1 1 1 1 0.336 0.336
Scenario B, rr cp 0.63 0.68 3 1 2 1 2 2 0.229 0.106
Scenario C, rr cp 0.63 0.68 3 2 3 2 2 2 -0.056 -0.166

*Severe* Disability, EDSS≥6

* EDSS means are derived from DMSRU records. EQ-5D health state levels for Scenarios A, B and C are simulated data.
Table 7. Rough Estimates of (1) Multiplicative “Conversion Factor E” which Converts Health Outcomes Measured as $E_{nEDSS-DYA}$ to $U_{EQ-5D-QALY}$, and (2) Multiplicative “Conversion Factor C/E” which Converts $C/E_{nEDSS-DYA}$ to $C/U_{EQ-5D-QALY}$, using Simulated Health State Levels for Three Scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>(1) “Mild” - “Severe” EQ-5D Score Differences (simulated data)</th>
<th>(2) “Severe” - “Mild” nEDSS Score Differences (DMSRU data)</th>
<th>(3) “Conversion Factor E” = Ratio of (1)/(2) = (EQ-5D score differences) / (nEDSS score differences)</th>
<th>(4) “Conversion Factor C/E” = 1/(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario A</td>
<td>$0.514 = 0.850 - 0.336$</td>
<td>$0.41 = 0.63 - 0.22$</td>
<td>$1.25$</td>
<td>$0.80$</td>
</tr>
<tr>
<td>Scenario B</td>
<td>$0.514 = 0.850 - 0.336$</td>
<td>$0.30 = 0.68 - 0.38$</td>
<td>$1.71$</td>
<td>$0.58$</td>
</tr>
<tr>
<td>Scenario C</td>
<td>$0.550 = 0.779 - 0.229$</td>
<td>$0.41 = 0.63 - 0.22$</td>
<td>$1.35$</td>
<td>$0.74$</td>
</tr>
<tr>
<td>Scenario D</td>
<td>$0.537 = 0.743 - 0.106$</td>
<td>$0.30 = 0.68 - 0.38$</td>
<td>$1.79$</td>
<td>$0.56$</td>
</tr>
</tbody>
</table>

* Table 6 is the source of data on differences in health outcome scores for ‘mild’ and ‘severe’ MS disability. nEDSS scores are computed from DMSRU records. EQ-5D scores in Scenarios A, B and C are simulated data.
V SUMMARY AND DISCUSSION

5.1 Clinical Overview of Betaseron® Treatment Consequences for Persons with MS

The reports of studies of Betaseron®, and its subsequent release for general use, have been a very heartening experience for clinicians who manage MS patients, and for the patients and their families. Although it is not “the answer”, it is an important first step, and the first drug released that appears to have an effect on the outcome of the disease.

It has been well tolerated, with minor but tolerable side effects. Of greater concern is the development of neutralizing antibodies in patients on the drug long term, which the initial reports suggest may decrease the long term effectiveness of the drug.

To a clinician the initial results are promising, and the possibility of greater benefit if the drug were used earlier is about to be tested. Because it appears to reduce the number and severity of acute attacks, reduce the rate of disability progression, and reduce disease activity within the nervous system on MRI, the drug appears to be a significant advance in the management of MS patients.

Finally, although the drug was studied in relapsing-remitting patients, it is reasonable to infer that benefit may also accrue to patients in the other patterns of MS (relapsing-progressive, chronic-progressive, benign, optic neuritis) even though the effects are much more difficult to measure in these groups because of the clinical and temporal pattern of their disease.

The last, and one of the most important, considerations in the use of this drug in patients is its cost. Another limiting factor is often the over expectation by patients about what the drug may do. Good patient education is required to explain what the drug has been demonstrated to do and what can be anticipated in terms of benefit.

5.2 C/E Analysis Results for Betaseron® in Multiple Sclerosis

The total health benefits per Pw MS who starts Betaseron® treatment shortly after onset of
symptoms at an early age is estimated to be about 1.4 nEDSS-DYA for females classified as relapsing-remitting at onset, equivalent to avoidance of 8% to 10% of all disability-weighted years expected over a 40 year MS natural history. This result is based on analyses of hypothetical onset cohorts of females with a definite diagnosis of relapsing-remitting or primary progressive MS at onset of symptoms, given a 15% Betaseron® treatment effect in slowing disability progression. MS disability progression data used in modelling the analysis life-tables data which describe EDSS progression in a Swedish MS onset cohort of 308 persons followed prospectively for 25 years. (Runmarker and Anderson, 1993) The size of expected total health benefits varies directly with treatment efficacy, and with the speed of MS disability progression, which varies by MS classification and by gender. When expressed as present values at time of MS onset (using a 5% discount rate) total treatment benefits fall to 0.5 nEDSS-DYA for females. These results are based on a two-endpoint model of MS progression, discussed in section 3.4.2, which substantially revise estimates reported in Tables 4.2 and 4.3 which are based on a one-endpoint model of MS progression.

Total costs for a Betaseron® treatment program are determined by the number of persons and annual costs per person treated. Program costs estimated for an MS onset cohort of 910 females classified as rr from onset total $355 million CDN over 40 years, where all PwMS classified as either rr are eligible for treatment and are treated from the third year after onset of MS until EDSS=6 is reached. These costs fall to $180 million when expressed as present values. Actual program costs are anticipated to be much less because eligibility for Betaseron® treatment is likely to be restricted, demand for treatment is likely to be less than 100%, and long term compliance is expected to be low, all of which reduces total program costs radically.

Cost / effectiveness assessments of Betaseron® in MS in this study use (normalized) EDSS-weighted Disability-Years-Avoided as the treatment outcome measure. C/E_{nEDSS-DYA} ratios for Betaseron® in MS are estimated for 15 scenarios, using a single-endpoint model of MS progression. Appropriate downward revisions to the estimates in Tables 4.3 and 4.3, by an order of magnitude of about 50%, are based on exploratory analyses using a two-endpoint model of MS progression and on other data revisions.

It is considered preferable to express C/E values as present values when treatment, health outcomes and costs and spread out over many years. When present values at time of onset of MS symptoms are calculated, the revised estimate of C/E_{nEDSS-DYA} for baseline Scenario #1 for rr females increases from $219,061 to $325,760 CDN. (Table 4.7) The discounted C/E_{nEDSS-DYA}
ratio rises because treatment costs are incurred immediately and continue for many years, while major treatment benefits are typically not realized for many years due to the slow rate of MS disability progression. $C/E_{nEDSS-DYA}$ estimates for Scenarios #2 - #5 are generally higher than those for baseline Scenario #1. $C/E$ ratios for Scenarios #7 - #13, which vary key values radically for purposes of sensitivity analyses, have a wide range. Estimates for Scenario #14, which models treatment of PwMS classified as primary progressive at onset, are substantially lower than Scenario #1 estimates for PwMS classified as relapsing-remitting at onset.

Even after account is taken of foreign exchange rate differences between CDN and US dollars, the revised $C/E_{nEDSS-DYA}$ estimates for Betaseron® fall in the middle and upper range of $C/E$ ratios estimated in 500 studies of life-saving interventions. (Tengs et al, 1995) See Appendix D below. $C/E_{nEDSS-DYA}$ estimates for Betaseron® would be revised downward further in analyses conducted from a societal perspective, rather than from a department of health perspective. The consequences of adopting a societal perspective may be substantial, but further research is required to verify this expectation.

The variables which dominate the $C/E$ analyses are 1) the long natural history of MS disability progression, 2) treatment efficacy in slowing the rate of disability progression, and 3) Betaseron® direct treatment costs per person with MS per year. The long natural history of relatively slow MS disability progression serves to dampen the $C/E$ ratio of preventive treatment, particularly when $C/E$ ratios are expressed as present values at time of MS onset. The magnitude of the efficacy effect on rate of disability progression determines total health outcomes. A doubling of the treatment efficacy would reduce the $C/E$ ratio by 50%. Betaseron®’s direct cost per PwMS treated per year dominates the size of estimated health care costs foregone due to treatment. A reductions in direct treatment costs by 50% would reduce total program costs and $C/E$ ratios by about the same proportion, when expressed in current dollars, and more than proportionately when expressed in present values. The size of $C/E_{nEDSS-DYA}$ estimates appears to be quite sensitive to how MS disability progression is modelled.

It is possible that even revised estimates $C/E$ ratios are biased upward, to an extent unknown, due to EDSS measurement deficiencies which inadequately scale relatively 'severe' MS-disability categories compared to relatively 'mild' MS-disability categories. If so then $E_{nEDSS-DYA}$ estimates treatment effects which slow MS progression are downward biased to an extent unknown, giving an upward bias to $C/E$ estimates.
It is also likely that C/E ratios based on studies which use \( E_{a\text{EDSS-DYA}} \) to measure treatment outcomes will be higher, and perhaps substantially higher, than C/E or C/U ratios based on studies which use more broadly-based indices of health status or utility to measure treatment outcomes. These broader measures include ambulation as one health dimension, so will capture the same types of treatment effects as the EDSS. In addition, broad-based health and utility indices include important health dimensions not adequately measured by the EDSS, which will measure treatment benefits not captured by \( E_{a\text{EDSS-DYA}} \). So it is likely that C/E and C/U studies which use more comprehensive measures of health outcomes will record larger total health outcomes (E) and utilities (U), which drive down C/E and C/U ratios. One qualification to be noted, however, is that adverse side effects and toxicities associated with treatment should also be included in analyses of net health outcomes, as is done using Q-TWiST methods. Using Q-TWiST methods, which give weight to both positive and negative dimensions of treatment outcomes, it becomes an empirical question as to whether or not C/E and C/U estimates based on nEDSS-DYA outcome measures are systematically higher than C/E and C/U estimates based upon more comprehensive health outcome measurement instruments.

Preliminary investigation of the relationship between EDSS scores and EuroQol scores suggests that if Betaseron\(^*\) treatment in slowing MS progression was analysed using a generic health outcome index, such as a EuroQol rather than \( E_{a\text{EDSS-DYA}} \), the resulting C/U ratios might be lower than \( C/E_{a\text{EDSS-DYA}} \) estimates by 25% or more.

\( C/E_{a\text{EDSS-DYA}} \) estimates of Betaseron\(^*\) in MS presented here are empirically founded in the availability of MS natural history data on MS disability progression (measured by EDSS), RCT treatment efficacy data (measured by EDSS), Betaseron\(^*\) treatment costs, and estimates of health costs foregone based on health care costs for 'mild' and 'severe' disability derived from population-based administrative data from Nova Scotia. With these data it is possible to model Betaseron\(^*\) therapeutic and economic consequences over 40 years following MS onset. Standard discounting methods are applied in order to express both health outcomes and costs as present values at time of onset.

\( C/E_{a\text{EDSS-DYA}} \) estimates suffer from being relatively narrow health status measures. Analyses based upon broader and more comprehensive approaches to both health outcomes and costs are preferable. Time, budget and data availability constraints precluded a broader approach in this study.
5.3 Total Program Costs in the Short and Long Run

Betaseron® program costs are dominated by direct treatment costs and by the number of PwMS who start and stay on treatment. C/E scenarios are presented which model vary 1) treatment eligibility criteria (eg, all PwMS, relapsing-remitting only, relapsing-remitting provided EDSS<6), 2) physician MS management decision (eg, discontinuing treatment following antibody development), patient demand for treatment (≤ 100%) and patient compliance (eg, 100%, 45% as per RCT rates, 20% long term rates), 3) treatment efficacy, 4) health care costs foregone and 5) co-payment policies (eg, zero, 20%). Total treatment program costs, expressed in current dollars, vary more or less proportionately with percentage changes modelled for these parameters. Total treatment program costs expressed in present values behave somewhat differently when parameter values are changed.

Betaseron® program costs per PwMS in a province are likely to be much greater in the short run than in the long run. Demand for treatment may be high initially, but will likely decline as compliance rates fall. Compliance studies find fairly rapidly declines in compliance rates, with long term rates for non-life-threatening conditions approaching 20%. (Coambs) Forecasting long term demand for treatment and long term compliance rates is a highly speculative exercise given the various uncertainties involved. However, sensitivity analyses provided within the 14 scenarios analysed in Chapter III demonstrate that patient demand and compliance variables are very important in determining total treatment program costs and, to a lesser extent, cost/effectiveness ratios.

The development of competing pharmacotherapies for MS are likely to reduce the cost of Betaseron® treatment programs, through both price reductions and loss of market share, but are unlikely to reduce the combined cost of all MS treatment programs.

5.4 Other MS Treatments of the Horizon

Interferon beta-1a (AVONEX) has been reported in relapsing-remitting as well as relapsing-progressive patients, treated for up to two years, to reduce the progression of the disease and a 32 percent reduction in relapse rate.
Another drug reported to reduce the number of relapses and the rate of progression has been Copolymer 1 (Copaxone). This drug has been submitted for assessment by the FDA. Other therapies under study include Linomide, Interferon beta-1a (Rebif), Tumor necrosis factor inhibitor (Tenefuse), oral myelin, Salazopyrin, Azathioprine and Methotrexate. Chomeric monoclonal antibody therapy to CD and T-cell vaccination for MS are also under study. (Bansil et al, 1995)

Each of these will require randomized clinical trial assessment, and subsequent cost effectiveness studies. Even more complicated, but possible, will be similar studies of combination therapies, similar to the pattern of advancement in the treatment of leukemia beginning some decades ago.

This may seem a daunting future but it is an exciting one and one that holds great promise for the management of MS patients. We believe that the tools are now available for the appropriate study of these drugs and the cost effectiveness of their application.
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APPENDIX A: Cost/Effectiveness Spreadsheet Model

1) Cost/Effectiveness Spreadsheet Glossary

**PwMS**: Person with Multiple Sclerosis

**Survivors**: PwMS remaining in the cohort

**Pr(Senior)**: Proportion of seniors (age $\geq$ 65) in the cohort

**Pr(Death)**: Cumulative probability of reaching EDSS 10 (death due to MS)

**Deaths**: Cumulative deaths among the cohort

**rr**: Relapsing Remitting

**cp**: Chronic Progressive

**Pr(rr)**: Probability of Relapsing Remitting Onset

**Nrr**: Number of PwMS classified as Relapsing Remitting

**Pr(EDSS<6)**: Probability of having an EDSS score less than 6

**Pr(EDSS>6)**: Probability of having an EDSS score $\geq$ 6

**Nrr<6**: Number of PwMS classified as rr with EDSS < 6

**Nrr>6**: Number of PwMS classified as rr with EDSS $\geq$ 6

**Pr(cp)**: Probability of Chronic Progressive Onset

**Ncp**: Number of PwMS classified as Chronic Progressive

**Ncp<6**: Number of PwMS classified as cp with EDSS < 6

**Ncp>6**: Number of PwMS classified as cp with EDSS $\geq$ 6

**Cost (EDSS<6)**: Health Care costs for PwMS with EDSS < 6

**Cost (EDSS>6)**: Health Care costs for PwMS with EDSS $\geq$ 6

**Cost (EDSS=10)**: Health Care costs in year of death for PwMS with EDSS 10

**Elig/Treat**: Eligibility/Management/ Demand factor

**Nrr{notE/T}**: Number rr not eligible or demanding treatment

**Nrr{E/T}**: Number rr eligible or demanding treatment

**Compliance**: Compliance factor

**E1.1**: Effectiveness factor ($0 \leq E1.1 \leq 1$), modifying Pr(EDSS>6)

**Nrr{E,T,C}**: Number rr eligible or demanding treatment and compliant

**Nrr{E,notC}**: Number rr eligible or demanding treatment, but not compliant

**Ncp{notE/T}**: Number cp not eligible or demanding treatment

**Ncp{E/T}**: Number cp eligible or demanding treatment

**Ncp{E,C,T}**: Number cp eligible or demanding treatment and compliant

**Betaseron**: Betaseron$^*$ treatment costs

**Health Care Cost (EDSS<6)**: Annual health care costs for PwMS less than EDSS 6

**Health Care Cost (EDSS>6)**: Annual health care cost for PwMS equal or greater than EDSS 6

**Total Health Care (NT)**: Total Health care costs for PwMS not receiving treatment

**Total Health Care (T)**: Total Health care costs for PwMS receiving treatment, excluding direct treatment costs

**Foregone HC Costs (NT-T)**: Annual foregone health care costs due to treatment

**Net Treatment Costs (T-FC)**: Annual direct treatment costs less foregone health care costs

**PV Treatment**: Present value of treatment costs at year of onset, $Y_0$

**PV HC (NT)**: Present Value of health care costs without treatment at year of onset, $Y_0$

**PV HC (T)**: Present Value of health care costs with treatment at year of onset, $Y_0$
PV FC (NT-T): Present value of foregone health care costs at year of onset, $Y_0$

PV (T-FC): Present value of net treatment costs at year of onset, $Y_0$

M, $rr$EDSS<6: Mean EDSS score for $rr$ less than EDSS 6 (source: NS MSID)

M, $rr$EDSS>6: Mean EDSS score for $rr$ equal or greater than EDSS 6 (source: NS MSID)

M, cpEDSS<6: Mean EDSS score for cp less than EDSS 6 (source: NS MSID)

M, cpEDSS>6: Mean EDSS score for cp equal or greater than EDSS 6 (source: NS MSID)

Total Dis Years: Total EDSS-weighted disability person-years for the cohort, $Y=0$ to 40

PV Total DY: Present value of total disability person-years at year of onset, $Y_0$

Nrr(NT)<6: Number of $rr$ less than EDSS 6 not receiving treatment

Nrr(T)<6: Number of $rr$ less than EDSS 6 receiving treatment

Nrr(NT)>6: Number of $rr$ equal or greater than EDSS 6 not receiving treatment

Nrr(T)>6: Number of $rr$ equal or greater than EDSS 6 receiving treatment

Ncp(NT)<6: Number of cp less than EDSS 6 not receiving treatment

Ncp(T)<6: Number of cp less than EDSS 6 receiving treatment

Ncp(NT)>6: Number of cp equal or greater than EDSS 6 not receiving treatment

Ncp(T)>6: Number of cp equal or greater than EDSS 6 receiving treatment

Deaths Avoided: Number EDSS 10 avoided due to treatment (equals zero in this analysis)

Total DY Avoided: Total EDSS disability person-years avoided due to treatment

PV Total DY: Present value of total avoided disability person-years

E2: Modifies probability of progression from relapsing remitting to chronic progressive
2) Cost/Effectiveness Spreadsheet Accounting Relationships

Note: time subscripts are omitted.

1) MS NATURAL HISTORY MODULE

1.0 \( N = N_{mortality} + N_{survivors} \\
= N_{PrDeath} + N(1-PrDeath) \\
= N_d + N_s \\
\\
1.1 \( N = N_d + N_s[(1-PrProgressive) + PrProgressive] \\
= N_d + N_s[(1-PrP) + PrP] \\
= N_d + N_s(1-PrP) + N_sPrP \\
= N_d + N_{rr} + N_p \\
\\
1.2 \( N = N_d + (N_{rr} + N_p)[(1-PrEDSS>=6) + PrEDSS>=6] \\
= N_d + [N_{rr}(1-PrEDSS>=6) + N_{rr}PrEDSS>=6] \\
+ [N_p](1-PrEDSS>=6) + N_pPrEDSS>=6] \\
= N_d + [N_{rr}<6 + N_{rr}>=6] + [N_p<6 + N_p>=6] \\
\\
2) HEALTH POLICIES MODULE

Models policy decisions regarding eligibility for treatment (Betaseron®). Policy embraces both public and private sector health insurance programs. Within the model policy may operate on who is eligible by MS classification (rr, cp), clinical criteria (EDSS < x; years since onset), age, gender and types of health care service benefits (MD, HOSP, PHARM, Betaseron®).

3) TREATMENT DEMAND AND COMPLIANCE MODULE

Models behavioural decisions by persons with MS regarding demand for treatment (Betaseron®) and compliance with prescribed treatment regimens in the short and long run, where the long run in this case involves lifetime compliance. The health policies module and treatment demand and compliance modules together determine the proportion of persons with MS receiving treatment, stratified by gender, MS classification, mild or severe EDSS disability, and year since onset. These modules operate in the model through probability of treatment vectors, PrT.

1.3 \( N = N_d + [(N_{rr}<6 + N_{rr}>=6) + [N_p<6 + N_p>=6)](PrT + (1-PrT)) \\
= N_d + [N_{rr}<6 + N_{rr}>=6] + [N_p<6 + N_p>=6][PrT] \\
+ [N_{rr}<6 + N_{rr}>=6] + [N_p<6 + N_p>=6][(1-PrT)] \\
= N_d + [N_{rr}<6 + N_{rr}>=6]PrT + [N_p<6 + N_p>=6]PrT \\
+ [N_{rr} + N_{rr6}](1-PrT) + [N_p<6 + N_p>=6](1-PrT) \\
= N_d + N_{rr}<6PrT + N_{rr}>=6PrT + N_p<6PrT + N_p>=6PrT \\
+ N_{rr}<6(1-PrT) + N_{rr}>=6(1-PrT) + N_p<6(1-PrT) + N_p>=6(1-PrT) \\
= N_d + N_{rr}<6T + N_{rr}>=6T + N_p<6T + N_p>=6T
\[ N_{r<6} + N_{r>6} + N_{p<6} + N_{p>6} \]
\[ = N_d + \left[ N_{r<6} + N_{r>6} + N_{p<6} + N_{p>6} \right] T \]
\[ + \left[ N_{r<6} + N_{r>6} + N_{p<6} + N_{p>6} \right] N_T \]

4) TREATMENT EFFICACY MODULE (Betaseron®)

**Treatment Efficacy (E)**, in outcome domains \( j = 1, \ldots, 7 \) \((E_j)\), is modelled to reflect expected treatment effects attained under RCT conditions. The efficacy variable \( E_j \) operates on health status domains measured during clinical trials. Domain #1 (our list) is MS progression as measured by variable \( \text{PrEDSS} \geq 6 \). A more complete portrayal of treatment efficacy would model treatment effects on other important health status domains, separately and jointly through an MS specific or global health status index.

**Compliance** \((C)\) modifies treatment efficacy achieved under RCT conditions by multiplying \( E_j \) by \( C \), a compliance rate with values from 0 to 1.0. A compliance rate of 1.0 (perfect compliance) is used to model maximum efficacy. Lower compliance rates may be entered to model effectiveness under real world conditions.

\[ N = N_d + \left[ N_{r<6} + N_{r>6} + N_{p<6} + N_{p>6} \right] T (E_1)(C) \]
\[ + \left[ N_{r<6} + N_{r>6} + N_{p<6} + N_{p>6} \right] N_T \]

5) HEALTH OUTCOMES MODULE

This module combines modules 1) - 4) to generate estimates of net health outcomes achieved as a result of treatment (Betaseron®). In the current model health outcomes are measured in terms of normalized EDSS-weighted disability years avoided, \( \text{nEDSS-DYA} \). More complete models would include other health status domains in net health outcomes.

6) TREATMENT AND HEALTH CARE COSTS MODULE, UTILIZERS

This module enters annual costs per person with MS for direct treatment costs (Betaseron®) and other direct public sector health care costs (MD/HOSP/PHARM), stratified by gender, MS classification and mild or severe EDSS disability. These annual costs per person are calculated on a per utilizer basis from Nova Scotia's data. Annual costs per utilizer and much higher than annual costs per persons with MS because only 27% of the population at risk has one or more hospital separations per year.

This module also uses modules 1) - 4) to estimate total treatment costs and health costs foregone as a result of treatment, using costs per utilizer.

7) TREATMENT AND HEALTH CARE COSTS MODULE, POPULATION AT RISK

This module is identical to module 6) except that it uses person with MS population at risk annual cost data.
8) PRESENT VALUES MODULE

Applies standard discounting methods using a 5% real discount rate as the baseline discount rate.

9) COST/EFFECTIVENESS MODULE

This module combines modules 1) - 9) to estimate cost / effectiveness ratios for treatment (Betaseron®) on both a utilizer and population at risk basis.
APPENDIX B: COST / EFFECTIVENESS RESULTS: DETAILED TABLES

Females

Cost/Effectiveness Modules (Based on Scenario One):
   2.1 MS Natural History Module
   2.2 Treatment Effectiveness Modules
   2.3 Cost Module, per Utilizer Basis
   2.4 Cost Module, Population-at-Risk Basis
   2.5 Cost/Effectiveness Results Module, per Utilizer Basis
   2.6 Cost/Effectiveness Results Module, population-at-Risk Basis

Note -
Appendix B in the 1996 report to CCOHTA included 110 pages of tables that detailed results for Females, Scenario 1, for each of the Cost/Effectiveness Modules 2.1 – 2.6. These pages are excluded from this 2003 Adobe Acrobat PDF file copy of the 1996 report to CCOHTA. Copies of the excluded pages may be obtained from the authors: murray.brown@dal.ca or chris.skedgel@cdha.nshealth.ca.
APPENDIX C: MS CLASSIFICATIONS: TRANSITION MATRICES, SUCCESSIVE VISITS

TRANSITION MATRIX OF MS CLASSIFICATION AT VISIT \( i \) BY VISIT \( (i+1) \)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Relapsing Remitting</th>
<th>Relapsing Progressive</th>
<th>Chronic Progressive</th>
<th>Benign</th>
<th>RBN Only</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing</td>
<td>552</td>
<td>129</td>
<td>48</td>
<td>80</td>
<td>1</td>
<td>810</td>
</tr>
<tr>
<td>Remitting</td>
<td>68.15</td>
<td>15.93</td>
<td>5.93</td>
<td>9.88</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Relapsing</td>
<td>91</td>
<td>280</td>
<td>146</td>
<td>5</td>
<td>0</td>
<td>522</td>
</tr>
<tr>
<td>Progressive</td>
<td>17.43</td>
<td>53.64</td>
<td>27.97</td>
<td>0.96</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>29</td>
<td>98</td>
<td>453</td>
<td>1</td>
<td>0</td>
<td>581</td>
</tr>
<tr>
<td>Progressive</td>
<td>4.99</td>
<td>16.87</td>
<td>77.97</td>
<td>0.17</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>78</td>
<td>11</td>
<td>8</td>
<td>89</td>
<td>0</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>41.94</td>
<td>5.91</td>
<td>4.30</td>
<td>47.85</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>RBN Only</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>50.00</td>
<td>25.00</td>
<td>0.00</td>
<td>0.00</td>
<td>25.00</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>752</td>
<td>519</td>
<td>655</td>
<td>175</td>
<td>2</td>
<td>2103</td>
</tr>
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</table>

Frequency Missing = 11


APPENDIX D  Tengs et al: C/E RESULTS FROM 500 STUDIES OF LIFE-SAVING INTERVENTIONS (excerpts)

Source:


Pages 378 – 384 from Tengs et al. were included in the 1996 Report, but are not reproduced here.

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